OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

CASWELL FILE

6

108102

SRRD/GCSB TRANSMITTAL SHEET FOR PART B's

Pesticide: Pirimiphos-Methyl

Transmitted to HED on 11/28/89 Chemical#/Case#:2535
Chem. Tox.#: 334B
Sponsor: ICI Americas

CRM: Ruby Whiters Phone#: 557-2557

This action contains a request for a DATA WAIVER ( )/ TIME EXTENSION ( ). Label attached: Yes ( )/ No (X)

Branch: Toxicology I, Section II Reviewer: W. B. Grogar
Completed: 3/22/90 Concurrence: [signature] 4/4/90

Response, by Guideline

Guideline #: 81-1 Description: Acute oral/rat
Compliance Codes: Y/1 Data Waiver ( )/ Time Extension ( )
MRID 00080726, Study # NA
Discussion: MRID # 00080726 is not in the bibliography. MRID # 0012657 was conducted on a 75.4% formulation Tox. Category III. MRID # 00164523 was conducted on a 40% formulation. Technical is 94.2%

Recommendation :A study conducted on the technical is required for review.

Guideline #: 81-2 Description: Acute Dermal/rat
Compliance Codes: Y/1 Data Waiver ( )/ Time Extension ( )
MRID 00080727, Study # NA
Discussion: MRID # 00080727 is not in the bibliography. MRID # 00126257 was conducted on a 75.4% formulation. Tox Category III. MRID # 00164523 was conducted on a 40% formulation. Technical is 94.2%.

Recommendation :A study conducted on the technical is required for review.

Guideline #: 81-3 Description: Acute Inhalation/rat
Compliance Codes: Y/1 Data Waiver ( )/ Time Extension ( )
MRID 00126258, Study # CTL/P/602
Discussion: MRID # 00126258 was not conducted on the technical. It was conducted on a 75.4% formulation. Tox category not established. Nominal concentration reported. Technical is 94.2%.

Recommendation :A study conducted on the technical is required for review.

Guideline #: 81-4 Description: Primary Eye Irritation/rabbit
Compliance Codes: Y/1 Data Waiver ( )/ Time Extension ( )
MRID 00164524, Study # CTL/P/1305
Discussion: MRID # 00164524 was conducted on a 40% formulation. MRID # 00126257 was conducted on a 75.4% formulation. Tox Category II for 75.4% formulation. MRID # 00080729 is not in the bibliography. Technical is 94.2%.

Recommendation :A study conducted on the technical is required for review.

Guideline #: 81-5 Description: Primary dermal irritation/rabbit
Compliance Codes: Y/1 Data Waiver ( )/ Time Extension ( )
MRID 00080728, Study # NA
Discussion: MRID # 00080728 is not in the bibliography. MRID # 00126257 conducted on a 75.4% formulation. Tox. Category IV. MRID # 00164524 was conducted on a 40% formulation. Technical is 94.2%.

Recommendation :A study conducted on the technical is required for review.

Guideline #: 81-6 Description: Dermal sensitization/guinea pig
Compliance Codes: Y/1 Data Waiver ( )/ Time Extension ( )
MRID 00129341 , Study # CTL/P/499
Discussion: DER of MRID # 00129341 has been examined and appears to be adequate (Core-Minimum).

Recommendation :The study MRID # 00129341 is acceptable for review.

Guideline #: 81-7 Description: Acute delayed neurotoxicity/hen
Compliance Codes: Y/1 Data Waiver ( )/ Time Extension ( )
MRID 00080721 , Study # NA
Discussion: MRID # 00080721 is not in the bibliography and the not in the one-liners. Two studies (#'s ICI/49/75220 and an unnumbered study dated 6/20/80) are present in Tox files. Both studies are unacceptable. Results were uninterpretable, but suggestive of a positive response.

Recommendation :A study is not needed because the 90-day neurotoxicity study supercedes the acute study.

Guideline #: 82-1(a) Description: 90-day feeding/rodent
Compliance Codes: Y/1 Data Waiver ( )/ Time Extension ( )
MRID 00080730 , Study # NA
Discussion: MRID #'s 00080730 and 00080745 are not in the bibliography. A 90-day rat study is listed in the one-liners. (Core-Minimum). The DER was examined but was too brief to determine the adequacy of study. However, the 2-Yr. chronic/oncogenicity study supercedes the requirement for this study.

Recommendation :The study is not needed for review if the chronic study is acceptable.

Guideline #: 82-1(b) Description: 90-day feeding/nonrodent
Compliance Codes: Y/1 Data Waiver ( )/ Time Extension ( )
MRID 00080742, Study # NA
Discussion: MRID's 00080742 and 00080743 are not in the bibliography. A 90-day dog study is listed in the one-liners. (Core-Minimum). The DER was examined but found to be too brief to determine the adequacy of the study. However, a 2-Yr. chronic study supercedes the requirement for the study.
Recommendation :The study is not needed for review if the chronic study is acceptable.

Guideline #: 82-2 Description: 21-day dermal/rodent/rabbit
Compliance Codes: Y/1 Data Waiver ( )/ Time Extension ( )
MRID 00129342, Study # 2279-38/59
Discussion: DER of MRID # 00129342 has been examined and appears to be adequate (Core-Minimum).

Recommendation :The study MRID # 00129342 is acceptable for review.

Guideline #: 82-3 Description: 90-day dermal/rodent
Compliance Codes: N/7 Data Waiver ( )/ Time Extension ( )
MRID NA, Study # NA
Discussion: The study is not required under current use patterns. Code 7 indicates "criteria not met".

Recommendation :A study is not needed.

Guideline #: 82-4 Description: 90-day inhalation/rodent
Compliance Codes: N/7 Data Waiver ( )/ Time Extension ( )
MRID NA , Study # NA
Discussion: A study is not required under current use patterns. Code 7 indicates "criteria not met".

Recommendation :A study is not needed.

Guideline #: 82-5(a) Description: 90-day neurotoxicity/hen
Compliance Codes: Y/1 Data Waiver ( )/ Time Extension ( )
MRID 00126254 , Study # ICI 411 NT/821118
Discussion: DER of MRID # 00126254 has been examined and appears to be acceptable (Core-Guideline).

Recommendation :The study MRID # 00126254 is acceptable for review.

Guideline #: 82-5(b) Description: 90-day neurotoxicity/ mammalian
Compliance Codes: N/7 Data Waiver ( )/ Time Extension ( )
MRID NA , Study # NA
Discussion: Code 7 indicates "criteria not met".

Recommendation :The study is not needed at this time.

Guideline #: 83-1(a) Description: Chronic feeding/rodent
Compliance Codes: Y/1 Data Waiver ( )/ Time Extension ( )
MRID 00081912 , Study # NA
Discussion: MRID # 00081912 was not in the bibliography. However, a 2-Yr. Chronic/Oncogenicity study is listed in the one liners. The DER has been examined (study # HO/IH/P/113; 6/74), but was too brief to determine the adequacy of the study. (Core-Minimum)
Recommendation :The study should be submitted for review after being reformatted.

Guideline #: 83-1(b) Description: Chronic feeding/nonrodent
Compliance Codes: Y/1 Data Waiver ( )/ Time Extension ( )
MRID 00080749 , Study # NA
Discussion: MRID # 00080749 is not in the bibliography. However, a 2-Yr Chronic study conducted by Huntingdon Reo on 5/8/73 is listed in the one-liners. DER of study was examined but is too brief to determine the adequacy of the study. (Core-Guideline).

Recommendation :The study should be submitted for review after being reformatted.

Guideline #: 83-2(a) Description: Oncogenicity/rat
Compliance Codes: Y/1 Data Waiver ( )/ Time Extension ( )
MRID 00081912 , Study # NA
Discussion: MRID # 00081912 is not in the bibliography. However, a 2-Yr Chronic/Oncogenic study is listed in the one-liners. The DER has been examined (study # HO/IH/P/113; 6/74), but was too brief to determine the adequacy of the study. (Core-Minimum).

Recommendation :The study should be submitted for review after being reformatted.

Guideline #: 83-2(b) Description: Oncogenicity/mouse
Compliance Codes: Y/1 Data Waiver ( )/ Time Extension ( )
MRID 00080746 , Study # NA
Discussion: MRID # 00080746 is not in the bibliography. An 18-Mo mouse study (# ICI 3417658; 7/15/76) is listed in the one-liners. The DER was examined but is too brief to determine the adequacy of the study. (Core-Minimum).

Recommendation :The study should be submitted for review after being reformatted.

Guideline #: 83-3(a) Description: Teratogenicity/rat
Compliance Codes: Y/1 Data Waiver ( )/ Time Extension ( )
MRID 00151623 , Study # CTL/P1334
Discussion: DER of MRID #00151623 has been examined and appears to be acceptable. (Core-Guideline).

Recommendation :The study MRID # 00151623 is acceptable for review.

Guideline #: 83-3 (b) Description: Teratogenicity/rabbit.
Compliance Codes: Y/1 Data Waiver ( )/ Time Extension ( )
MRID 00080734 , Study # NA

Discussion: MRID # 00080734 is not in the bibliography. However, a rabbit study is listed in the one-liners (study # HO/CTL/P/119B). (Core-Minimum) DER of the study has been examined, but is too brief to determine the adequacy of the study.

Recommendation:The study MRID # 00080734 should be reformatted and submitted for review.

Guideline #: 83-3(c) Description: Teratogenicity/mouse
Compliance Codes: NA/NA Data Waiver ( )/ Time Extension ( )
MRID NA , Study # NA
Discussion: NA

Recommendation :NA

Guideline #: 83-4 Description: 3-generation reprod./rat
Compliance Codes: Y/1 Data Waiver ( )/ Time Extension ( )
MRID 00080735 , Study # 5457/72/853
Discussion: MRID #'s 00080735 and 00080736 are not in the bibliography. One study # ICI 63/76534, 8/31/76 is listed in the one-liners and is Core-Minimum. A second study # 5457/72/853) is in a Tox memo 2/21/80 and is Core-Minimum. The DER's have been examined but contain too little detail to determine if the studies are adequate.

Recommendation :The two studies MRID #'s 00080735 and 00080736 should be submitted for review after being reformatted.

Guideline #: 84-2(a) Description: Gene mutation/Ames
Compliance Codes: Y/1 Data Waiver ( )/ Time Extension ( )
MRID 00144969 , Study # (TL/P/962
Discussion: DER of MRID # 00144969 has been examined and appears to be acceptable. (Acceptable)

Recommendation :The study MRID # 00144969 is acceptable for review.

Guideline #: 84-2(b) Description: Struct. chrom. aberration
Compliance Codes: Y/1 Data Waiver ( )/ Time Extension ( )
MRID 00126256 , Study # NA
Discussion: MRID's 00126256 and 00080733 are not in the bibliography. A cytogenetic study in rats (study # 412212, 5/80) is in the one-liners. (No Core-Grade.) DER was examined but was too brief to determine the adequacy of the study.

Recommendation :The studies should be submitted for review after being reformatted.

Guideline #: 84-2(c) Description: Other genotoxic effects
Compliance Codes: Y/4 Data Waiver ( )/ Time Extension ( )
MRID NA , Study # NA
Discussion: A new study will be submitted. This is a data gap.

Recommendation :The new study will be acceptable for review.

Guideline #: 85-1 Description: General metabolism/rat
Compliance Codes: Y/1 Data Waiver ( )/ Time Extension ( )
MRID 00129345 , Study # ICI 299/79565
Discussion: MRID #'s 00080738 and 00080737 are not in the bibliography. DER of MRID # 00129345 has been examined and appears to be a low-dose repeated-dose study. The single low-and high-dose sections of the metabolism study have not been conducted. (Core-Minimum.)

Recommendation :The studies need to be submitted for review after reformatting.

Guideline #: 85-2 Description: Dermal penetration
Compliance Codes: N/7 Data Waiver ( )/ Time Extension ( )
MRID NA , Study # NA
Discussion: Code 7 indicates "Criteria not met". However, It was once proposed to use the chemical to control fleas on carpets. Tox decided, after receiving an exposure assessment, that a dermal penetration study is necessary.

Recommendation :The study will be needed if the once proposed use for carpet treatment to control fleas is pursued.

Guideline #: 86-1 Description: Domestic animal safety
Compliance Codes: N/NA Data Waiver ( )/ Time Extension ( )

MRID NA , Study # NA

Discussion: The sponsor failed to indicate a response. However, it was once proposed to use the chemical to control fleas on carpets. Domestic animals would probably receive a significant exposure.

Recommendation : The study will be needed on the end-use product if the once proposed use for carpet treatment control fleas is pursued.

MRID 42174

81-1 Acute Oral Toxicity in the Rat

ACCEPTANCE CRITERIA

Does your study meet the following acceptance criteria?:

1. NO **Technical form of the active ingredient tested. (for reregistration only)** 40% acute
2.* ____ **At least 5 young adult rats/sex/group**
3. ____ **Dosing, single oral.**
4.* NR **Vehicle control if other than water.** not tested
5. ____ **Doses tested, sufficient to determine a toxicity category or a limit dose (5000 mg/kg).**
6. ____ **Individual observations for the entire day of dosing.**
7. ____ **Observation period to last at least 14 days, or until all test animals appear normal whichever is longer.**
8. ____ **Individual daily observations.**
9.* ____ **Individual body weights.**
10.* NO **Gross necropsy on all animals.** - selected animals

Study can be substituted for one conducted with the technical product.

Criteria marked with a * are supplemental and may not be required for every study.

81-2 Acute Dermal Toxicity in the Rat, Rabbit or Guinea Pig

ACCEPTANCE CRITERIA

Does your study meet the following acceptance criteria?:

1. ___ Technical form of the active ingredient tested. (for reregistration only)
2.* ___ At least 5 animals/sex/group
3.* ___ Rats 200-300 gm, rabbits 2.0-3.0 kg or guinea pigs 350-450 gm.
4. ___ Dosing, single dermal.
5. ___ Dosing duration at least 24 hours.
6.* ___ Vehicle control, only if toxicity of vehicle is unknown.
7. ___ Doses tested, sufficient to determine a toxicity category or a limit dose (2000 mg/kg).
8. ___ Application site clipped or shaved at least 24 hours before dosing
9. ___ Application site at least 10% of body surface area.
10. ___ Application site covered with a porous nonirritating cover to retain test material and to prevent ingestion.
11. ___ Individual observations for the entire day of dosing.
12. ___ Observation period to last at least 14 days, or until all test animals appear normal whichever is longer.
13. ___ Individual daily observations.
14.* ___ Individual body weights.
15.* ___ Gross necropsy on all animals.

Waiver requested but can not be granted based on information provided by the sponsor.

Criteria marked with a * are supplemental and may not be required for every study.

STUDY # 01-

81-3 Acute Inhalation Toxicity in the Rat

ACCEPTANCE CRITERIA

Does your study meet the following acceptance criteria?:

1. ✓ Technical form of the active ingredient tested. (for reregistration only) 90 + %
2. ✓ Product is a gas, a solid which may produce a significant vapor hazard based on toxicity and expected use or contains particles of inhalable size for man (aerodynamic diameter 15 um or less).
3.* ✓ At least 5 young adult rats/sex/group
4.* ✓ Dosing, at least 4 hours by inhalation.
5.* ✓ Chamber air flow dynamic, at least 10 air changes/hour, at least 19% oxygen content.
6. no Chamber temperature, 22° C (±2°), relative humidity 40-60%. RH ranged from 25 - 40 %
7. ✓ Monitor rate of air flow
8. ✓ Monitor actual concentrations of test material in breathing zone.
9. ✓ Monitor aerodynamic particle size for aerosols.
10. ✓ Doses tested, sufficient to determine a toxicity catagory or a limit dose (5 mg/L actual concentration of respirable substance).
11. ✓ Individual observations for the entire day of dosing.
12. ✓ Observation period to last at least 14 days, or until all test animals appear normal whichever is longer.
13. ✓ Individual daily observations.
14.* ✓ Individual body weights.
15.* ✓ Gross necropsy on all animals.

Criteria marked with a * are supplemental and may not be required for every study.

MRID
Study # FIB 3241

81-4 Primary Eye Irritation in the Rabbit

ACCEPTANCE CRITERIA

Does your study meet the following acceptance criteria?:

1. N/A Technical form of the active ingredient tested. (for reregistration only) - Not a dust issue
2. Y Study not required if material is corrosive, causes severe dermal irritation or has a pH of ≤ 2 or ≥ 11.5.
3.* Y 6 adult rabbits
4. Y Dosing, instillation into the conjunctival sac of one eye per animal.
5.* Y Dose, 0.1 ml if a liquid; 0.1 ml or not more than 100 mg if a solid, paste or particulate substance.
6. Y Solid or granular test material ground to a fine dust. (material already a dust)* Same
7. Y Eyes not washed for at least 24 hours.
8. Y Eyes examined and graded for irritation before dosing and at 1, 24, 48 and 72 hr, then daily until eyes are normal or 21 days (whichever is shorter).
9. Y Individual observations for the entire day of dosing.
10. Y Individual daily observations.

Need study w/TGAI. Reasons given to support waiver do not apply to 1° eye irritation study.
of 81-1

Criteria marked with a * are supplemental and may not be required for every study.

Study F

81-5 Primary Dermal Irritation Study
ACCEPTANCE CRITERIA

Does your study meet the following acceptance criteria?:

1. no — Technical form of the active ingredient tested. (for reregistration only) 40% dust
2. X — Study not required if material is corrosive or has a pH of ≤ 2 or ≥ 11.5.
3.* X — 6 adult animals.
4. X — Dosing, single dermal.
5. X — Dosing duration 4 hours.
6. X — Application site shaved or clipped at least 24 hour prior to dosing.
7. X — Application site approximately 6 cm^2.
8. X — Application site covered with a gauze patch held in place with nonirritating tape
9. X — Material removed, washed with water, without trauma to application site
10. no — Application site examined and graded for irritation at 1, 24, 48 and 72 hr, then daily until normal or 14 days (whichever is shorter). (1, 22, 49 and 67 hours)
11. X — Individual observations for the entire day of dosing.
12. X — Individual daily observations.

Sponsor will need study with TGAI

Criteria marked with a * are supplemental and may not be required for every study.

STUDY F

81-6 Dermal Sensitization in the Guinea Pig

ACCEPTANCE CRITERIA

Does your study meet the following acceptance criteria?:

1. ✓ Technical form of the active ingredient tested. (for reregistration only)
2. N. Study not required if material is corrosive or has a pH of ≤ 2 or ≥ 11.5.
3. ✓ One of the following methods is utilized;
   - ___ Freund's complete adjuvant test
   - ___ Guinea pig maximization test
   - ___ Split adjuvant technique
   - ✓ Buehler test
   - ___ Open epicutaneous test
   - ___ Maur optimization test
   - ___ Footpad technique in guinea pig
   - ___ Other test accepted by OECD (specify)_____
4. ✓ Complete description of test
5. ✓ Reference for test.
6. ✓ Test followed essentially as described in reference document.
7. no Positive control included. positive control not used in this study. Information exists on separate study in which positive control was used with the Buehler procedure.

Criteria marked with a * are supplemental and may not be required for every study.

81-7 Acute Neurotoxicity in the Hen

ACCEPTANCE CRITERIA

Does your study meet the following acceptance criteria?:

1. ____ Study performed on an organophosphate cholinesterase inhibiting compound.
2. ____ Technical form of the active ingredient tested.
3. *____ Positive control utilized.
4. ____ Species utilized, domestic laying hen 8-14 months of age.
5. ____ Dosing oral by gavage or capsule (dermal or inhalation may be used).
6. ____ An acute oral LD_{50} is determined.
7. ____ Dose tested equal to an acute oral LD_{50} or a limit test of 5000 mg/kg.
8. *____ Dosed animals may be protected with atropine and/or 2-PAM.
9. ____ Sufficient test animals so that at least 6 survive.
10. ____ Negative (vehicle) control group of at least 6 hens
11. *____ Positive control of at least 4 hens. (if used)
12. ____ Test dose repeated if no signs of delayed neurotoxicity observed by 21 days after dosing.
13. ____ Observation period 21 days after each dose.
14. ____ Individual daily observations.
15. ____ Individual body weights.
16. *____ Individual necropsy not required.
17. ____ Histopathology performed on all animals. Tissue to be fixed in situ using whole animal perfusion techniques. At least three sections of each of the following tissues:

    ____brain, including medulla oblongata
    ____spinal cord; upper cervical, mid-thoracic and lumbro-sacral regions
    ____*tibial nerve; proximal regions and branches*
    ____sciatic nerve

Criteria marked with a * are supplemental and may not be required for every study.

82-1 Subchronic Feeding in the Rodent and Nonrodent

ACCEPTANCE CRITERIA

Does your study meet the following acceptance criteria?:

1. ____ Technical form of the active ingredient tested.
2. ____ At least 10 rodents or 4 nonrodents/sex/group (3 test groups and control group).
3. ____ Dosing duration daily for 90-days or 5 days/week for 13 weeks.
4. ____ Doses tested include signs of toxicity at high dose but no lethality in nonrodents or a limit dose if nontoxic (1000 mg/kg).
5. ____ Doses tested include a NOEL.
6. *____ Analysis for test material stability, homogeneity and concentration in dosing medium
7. ____ Individual daily observations.
8. ____ Individual body weights.
9. ____ Individual or cage food consumption.
10. *____ Opthalmoscopic examination (at least pretest and at term) control and high dose.
11. ____ Clinical pathology data of 12 & 13 at termination for rodents, before, monthly or midway and at termination for nonrodents.
12. ____ Hematology.
    - ____ Erythrocyte count
    - ____ Hemoglobin
    - ____ Hematocrit
    - ____ Leucocyte count
    - *____ Differential count
    - ____ Platelet count (or clotting measure)
13. ____ Clinical chemistry.
    - ____ Alkaline phosphatase
    - ____ Aspartate aminotransferase
    - *____ Creatinine kinase
    - ____ Lactic dehydrogenase
    - ____ Glucose
    - ____ Bilirubin
    - ____ Cholesterol
    - *____ Creatinine
    - ____ Total Protein
    - ____ Albumin
    - ____ Urea
    - ____ Inorganic phosphate
    - ____ Calcium
    - *____ Potassium
    - ____ Sodium
    - *____ Chloride
14. *____ Urinalysis, only when indicated by expected or observed activity. As scheduled in 11.
    - ____ Blood
    - ____ Protein
    - ____ Ketone bodies
    - ____ Appearance
    - ____ Glucose
    - ____Total bilirubin
    - *____ Urobilirubin
    - ____ Sediment
    - ____ Specific gravity (osmolality)
    - *____ Volume
15. ____ Individual necropsy of all animals.
16. ____ Histopathology of the following tissues performed on all nonrodents and rodents, all control and high dose animals, all animals that died or were killed on study, all gross lesions on all animals, target organs on all animals and lungs, liver and kidneys on all other animals.

Criteria marked with a * are supplemental and may not be required for every study.

____ aorta	____ jejunum	____ peripheral nerve
____ eyes	____ bone marrow	____ kidneys†
____ caecum	____ liver†	____ esophagus
____ colon	____ lung†	____ ovaries†
____ duodenum	____ lymph nodes	____ oviduct
____ brain†	____ stomach	____ pancreas
____ skin	____ mammary gland	____ rectum
____ heart†	____ spleen†	____ spinal cord (3x)
____ testes†	____ musculature	____ thyroid / parathyroids
____ pituitary	____ epididymis	____ salivary glands
____ ileum	____ adrenals†	____thymus
____ trachea	____ uterus	____urinary bladder

† organs to be weighed

Criteria marked with a * are supplemental and may not be required for every study.

82-2 Repeated Dose Dermal Toxicity (21-day) in the Rat, Rabbit or Guinea Pig

ACCEPTANCE CRITERIA

Does your study meet the following acceptance criteria?:

1. ___ Technical form of the active ingredient tested.
2. ___ At least 5 animals/sex/group (3 test groups and control group).
3. ___ Dosing duration at least 6 hour/day for 21 days or 5 days/week for 3 weeks.
4. ___ Application site at least 10% of body surface area.
5. ___ Doses tested include signs of toxicity at high dose, no or minimal dermal irritation, minimal lethality or a limit dose (1000mg/kg) if nontoxic.
6. * no Doses tested include a NOEL.
7. ___ Individual daily observations.
8. ___ Individual body weights.
9. ___ Individual or cage food consumption.
10. no Clinical pathology data of 11 & 12 at termination.
11. ___ Hematology.
    - ___ Erythrocyte count
    - ___ Hemoglobin
    - ___ Hematocrit
    - ___ Leucocyte count
    - * ___ Differential count
    - ___ Platelet count (or clotting measure)
12. ___ Clinical chemistry.
    - ___ Alkaline phosphatase
    - ___ Aspartate aminotransferase
    - * no Creatinine kinase
    - ___ Lactic dehydrogenase
    - ___ Glucose
    - ___ Bilirubin
    - ___ Cholesterol
    - * no Creatinine
    - ___ Total Protein
    - ___ Albumin
    - ___ Urea
    - no Inorganic phosphate
    - ___ Calcium
    - * ___ Potassium
    - ___ Sodium
    - * ___ Chloride
13. * no Urinalysis, only when indicated by expected or observed activity. As scheduled in 10.
    - ___ Blood
    - ___ Protein
    - ___ Ketone bodies
    - ___ Appearance
    - ___ Glucose
    - ___ Total bilirubin
    - * ___ Urobilirubin
    - ___ Sediment
    - ___ Specific gravity (osmolality)
    - * ___ Volume
14. ___ Individual necropsy of all animals.
15. ___ Histopathology performed on all control and high dose animals, all animals that died or were killed on study consisting of all gross lesions on all animals, target organs on all animals (to determine a NOEL), and skin (normal and treated) lungs, liver and kidneys.

Criteria marked with a * are supplemental and may not be required for every study.

82-3 Repeated Dose Dermal Toxicity (90-day) in the Rat, Rabbit or Guinea Pig

ACCEPTANCE CRITERIA

Does your study meet the following acceptance criteria?:

1. ____ Technical form of the active ingredient tested.
2. ____ At least 10 animals/sex/group (3 test groups and control group).
3. ____ Dosing duration at least 6 hour/day daily for 90 days or 5 days/week for 13 weeks.
4. ____ Application site at least 10% of body surface area.
5. ____ Doses tested include signs of toxicity at high dose, no or minimal dermal irritation, minimal lethality or a limit dose (1000mg/kg) if nontoxic.
6. *____ Doses tested include a NOEL.
7. ____ Individual daily observations.
8. ____ Individual body weights.
9. ____ Individual or cage food consumption.
10. *____ Opthalmoscopic examination (at least pretest and at term) control and high dose.
11. ____ Clinical pathology data of 12 & 13 in all animals at termination.
12. ____ Hematology.
    - ____ Erythrocyte count
    - ____ Hemoglobin
    - ____ Hematocrit
    - ____ Leucocyte count
    - *____ Differential count
    - ____ Platelet count (or clotting measure)
13. ____ Clinical chemistry.
    - ____ Alkaline phosphatase
    - ____ Aspartate aminotransferase
    - *____ Creatinine kinase
    - ____ Lactic dehydrogenase
    - ____ Glucose
    - ____ Bilirubin
    - ____ Cholesterol
    - *____ Creatinine
    - ____ Total Protein
    - ____ Albumin
    - ____ Urea
    - ____ Inorganic phosphate
    - ____ Calcium
    - *____ Potassium
    - ____ Sodium
    - *____ Chloride
14. *____ Urinalysis, only when indicated by expected or observed activity. As scheduled in 11.
    - ____ Blood
    - ____ Protein
    - ____ Ketone bodies
    - ____ Appearance
    - ____ Glucose
    - ____ Total bilirubin
    - *____ Urobilirubin
    - ____ Sediment
    - ____ Specific gravity (osmolality)
    - *____ Volume
15. ____ Individual necropsy of all animals.
16. ____ Histopathology of the following tissues performed on all nonrodents and rodents, all control and high dose animals, all animals that died or were killed on study, all gross lesions on all animals, target organs on all animals and lungs, liver and kidneys on all other animals.
    - ____ aorta
    - ____ eyes
    - ____ jejunum
    - ____ bone marrow
    - ____ peripheral nerve
    - ____ kidneys‡

Criteria marked with a * are supplemental and may not be required for every study.

____ caecum	____ liver†	____ esophagus
____ colon	____ lung†	____ ovaries†
____ duodenum	____ lymph nodes	____ oviduct
____ brain†	____ stomach	____ pancreas
____ skin	____ mammary gland	____ rectum
____ heart†	____ spleen†	____ spinal cord (3x)
____ testes†	____ musculature	____ thyroid / parathyroids
____ pituitary	____ epididymis	____ salivary glands
____ ileum	____ adrenals†	____ thymus
____ trachea	____ uterus	____ urinary bladder

† organs to be weighed

Criteria marked with a * are supplemental and may not be required for every study.

82-4 Subchronic Inhalation Toxicity (90-day) in the Rat

ACCEPTANCE CRITERIA

Does your study meet the following acceptance criteria?:

1. ____ Technical form of the active ingredient tested. (for reregistration only)
2. ____ Product is a gas, a solid which may produce a significant vapor hazard based on toxicity and expected use or contains particles of inhalable size for man (aerodynamic diameter 15 um or less).
3. ____ At least 10 young adult rats/sex/group
4. ____ Dosing, 6 hours per day, 5 days per week for 13 weeks.
5. ____ Food and water should be withheld during dosing.
6. •____ Chamber air flow dynamic, at least 10 air changes/hour, at least 19% oxygen content.
7. ____ Chamber temperature, 22° C (±2°), relative humidity 40-60%.
8. •____ Alternatively, oro-nasal or head only exposures may be used.
9. ____ Monitor rate of air flow,
10. ____ Monitor actual concentrations of test material in breathing zone.
11. ____ Monitor aerodynamic particle size for aerosols.
12. ____ Individual daily observations.
13. ____ Individual body weights.
14. ____ Individual or cage food consumption.
15. •____ Opthalmoscopic examination (at least pretest and at term) control and high dose.
16. ____ Clinical pathology data of 17 & 18 in all animals at termination.
17. ____ Hematology.
    - ____ Erythrocyte count
    - ____ Hemoglobin
    - ____ Hematocrit
    - ____ Leucocyte count
    - •____ Differential count
    - ____ Platelet count (or clotting measure)
18. ____ Clinical chemistry.
    - ____ Alkaline phosphatase
    - ____ Aspartate aminotransferase
    - •____ Creatinine kinase
    - ____ Lactic dehydrogenase
    - ____ Glucose
    - ____ Bilirubin
    - ____ Cholesterol
    - •____ Creatinine
    - ____ Total Protein
    - ____ Albumin
    - ____ Urea
    - ____ Inorganic phosphate
    - ____ Calcium
    - •____ Potassium
    - ____ Sodium
    - •____ Chloride
19. •____ Urinalysis, only when indicated by expected or observed activity. As scheduled in 16.
    - ____ Blood
    - ____ Protein
    - ____ Ketone bodies
    - ____ Appearance
    - ____ Glucose
    - ____ Total bilirubin
    - •____ Urobilirubin
    - ____ Sediment
    - ____ Specific gravity (osmolality)
    - •____ Volume

Criteria marked with a • are supplemental and may not be required for every study.

20. ____ Individual necropsy of all animals.

21. ____ Histopathology of the following tissues performed on all nonrodents and rodents, all control and high dose animals, all animals that died or were killed on study, all gross lesions on all animals, target organs on all animals and lungs, liver and kidneys on all other animals.

____ aorta	____ jejunum	____ peripheral nerve
____ eyes	____ bone marrow	____ kidneys†
____ caecum	____ liver†	____ esophagus
____ colon	____ lung†	____ ovaries†
____ duodenum	____ lymph nodes	____ oviduct
____ brain†	____ stomach	____ pancreas
____ skin	____ mammary gland	____ rectum
____ heart†	____ spleen†	____ spinal cord (3x)
____ testes†	____ musculature	____ thyroid / parathyroids
____ pituitary	____ epididymis	____ salivary glands
____ ileum	____ adrenals†	____ thymus
____ trachea	____ uterus	____ urinary bladder

† organs to be weighed

82-5 Subchronic Neurotoxicity (90-day) in the Hen

ACCEPTANCE CRITERIA

Does your study meet the following acceptance criteria?:

1. ___ Study performed on an organophosphate cholinesterase inhibiting compound.
2.* ___ Technical form of the active ingredient tested.
3. ___ Positive control utilized. (recommended but optional)
4. ___ Species utilized, domestic laying hen 8-14 months of age.
5. ___ At least 10 animals/sex/group [3 test groups, a positive control (optional) and a negative (vehicle) control group].
6. ___ Dosing duration at least daily for 90 days or 5 days/week for 13 weeks.
7. ___ Dose route oral gavage or capsule. (dermal or inhalation may be appropriate)
8. ___ Doses tested include signs of toxicity at high dose, no or minimal lethality
9.* ___ Doses tested include a NOEL.
10. ___ Individual daily observations.
11. ___ Individual body weights.
12. ___ Individual or cage food consumption.
13.* ___ Individual necropsy not required.
14. ___ Histopathology performed on all animals. Tissue to be fixed in situ using whole animal perfusion techniques. At least three sections of each of the following tissues:

___ brain, including medulla oblongata
___ spinal cord; upper cervical, mid-thoracic and lumbro-sacral regions
No ___ tibial nerve; proximal regions and branches — tibial n., distal branches examined
___ sciatic nerve

Criteria marked with a * are supplemental and may not be required for every study.

83-1 Chronic Feeding in the Rodent and Nonrodent

ACCEPTANCE CRITERIA

Does your study meet the following acceptance criteria?:

1. ✓ Technical form of the active ingredient tested.
2. ✓ At least 20 rodents or 4 nonrodents/sex/group (3 test groups and control group).
3. ✓ Dosing duration in rodents minimum 12 month nonfood use, 24 months food use; in nonrodents minimum 12 months[1].
4. no Doses tested include signs of toxicity at high dose but no lethality in nonrodents or a limit dose if nontoxic (1,000 mg/kg). one death at HDT
5. • no Doses tested include a NOEL. low dose inhibits plasma chol
6. • no Analysis for test material stability, homogeneity and concentration in dosing medium
7. ✓ Individual daily observations.
8. ✓ Individual body weights.
9. ✓ Individual or cage food consumption.
10. • ✓ Opthalmoscopic examination (at least pertest and at term) control and high dose.
11. ✓ Clinical pathology data for all nonrodents and at least 10 rodents/group consisting of 12, 13 & 14.
13. ✓ Hematology at 6 month intervals consisting of at least;
    - ✓ Erythrocyte count
    - ✓ Hemoglobin
    - ✓ Hematocrit
    - ✓ Leucocyte count
    - • ✓ Differential count
    - ✓ Platelet count (or clotting measure)
14. ✓ Clinical chemistry at 6 month intervals consisting of at least;
    - ✓ Alkaline phosphatase
    - no Aspartate aminotransferase
    - • no Creatinine kinase
    - no Lactic dehydrogenase
    - ✓ Glucose
    - ✓ Bilirubin
    - ✓ Cholesterol
    - • no Creatinine
    - ✓ Total Protein
    - ✓ Albumin
    - ✓ Urea
    - no Inorganic phosphate
    - no Calcium
    - • ✓ Potassium
    - ✓ Sodium
    - • no Chloride
15. Urinalysis at 6 month intervals consisting of at least;
    - no Blood
    - ✓ Protein
    - ✓ Ketone bodies
    - no Appearance
    - ✓ Glucose
    - no Total bilirubin
    - • ✓ Urobilirubin
    - ✓ Sediment
    - ✓ Specific gravity (osmolality)
    - • ✓ Volume
16. ✓ Individual necropsy of all animals.
17. ✓ Histopathology of the following tissues performed on all nonrodents and rodents, all control and high dose animals, all animals that died or were killed on study, all gross lesions on all animals, target organs on all animals and lungs, liver and kidneys on all other animals.

Criteria marked with a • are supplemental and may not be required for every study.

___ eyes	___ bone marrow	___ kidneys†
___ caecum	___ liver†	___ esophagus
___ colon	___ lung†	___ ovaries†
___ duodenum	___ lymph nodes	___ oviduct
___ brain†	___ stomach	___ pancreas
___ skin	___ mammary gland	___ rectum
___ heart†	___ spleen†	___ spinal cord (3x)
___ testes†	___ musculature	___ thyroid / parathyroids
___ pituitary	___ epididymis	___ salivary glands
___ ileum	___ adrenals†	___ thymus
___ trachea	___ uterus	___ urinary bladder

† organs to be weighed

Six month dog studies may be acceptable. (?)

Criteria marked with a * are supplemental and may not be required for every study.

83-2 Oncogenicity in Rats or Mice

ACCEPTANCE CRITERIA

1. ✓ Technical form of the active ingredient tested.
2. ✓ At least 50 animals/sex/group (3 test groups and control group).
3. ✓ Dosing duration is at least 18 months for mice and 24 months for rats.
4. ___ Number of survivors in any group does not fall below 50% at 15 months for mice, 18 months for rats or 25% at 18 months for mice, 24 months for rats.
5. ‡ ___ Doses tested include an MTD or limit dose if nontoxic (1,000 mg/kg).
6. * no Doses tested include a NOEL for systematic effects.
7. * no ✓ Analysis for test material stability, homogeneity and concentration in dosing medium
8. ✓ Individual daily observations.
9. ✓ Individual body weights.
10. ✓ Individual or cage food consumption.
11. ✓ Individual necropsy of all animals.
12. no Blood smear from 10 animals/sex/dose at 12 and 18 months and termination. Differential count high dose and controls, all other doses if high dose shows pathology. only at 18 mos
13. no Histopathology of the following tissues performed on all interim sacrifice animals, all control and high dose animals, all animals that died or were killed on study, all gross lesions on all animals, target organs on all animals and lungs, liver and kidneys on all other animals.

✓ aorta	✓ jejunum	✓ peripheral nerve
✓ eyes	___ bone marrow	___ kidneys†
✓ caecum	✓ liver†	✓ esophagus
✓ colon	✓ lung†	___ ovaries†
___ duodenum	___ lymph nodes	no oviduct
___ brain†	✓ stomach	___ pancreas
✓ skin	✓ mammary gland	___ rectum
✓ heart†	___ spleen†	no spinal cord (3x)
✓ testes†	✓ musculature	✓ thyroid / parathyroids
___ pituitary	___ epididymis	✓ salivary glands
✓ ileum	___ adrenals†	___ thymus
✓ trachea	✓ uterus	___ urinary bladder

histopath only conducted when gross lesions were present for ✓ 31 organs

† organs to be weighed no organs weighed

‡ The position document entitled "Selection of a Maximum Tolerated Dose (MTD) in Oncogenicity Studies (EPA No. 540/09-88-003) stated EPA's criteria for determining if an oncongenicity study has been adequately performed in terms of doses tested. However OPP is also aware that older oncogenicity studies, upon initial review or re-review, may have been tested at doses lower than the predicted MTD. In the event that such testing appears to be at doses less than the predicted MTD, the Office of Pesticides Program has been reviewing and

Criteria marked with a * are supplemental and may not be required for every study.

considering the entire weight of the evidence to determine if retesting is necessary. Certain factors which affect the agency's decision to retest include but are not limited to the following: demonstrated oncogenicity in another species, nearness to the apparent MTD, genotoxic effects, structure-activity factors, absolute value of the highest dose tested and metabolic considerations.

Study: 102-212

83-3 Teratology Studies

ACCEPTANCE CRITERIA

Does your study meet the following acceptance criteria?:

Rat rabbit

1. ✓ ✓ Technical form of the active ingredient tested.
2. ~~No~~ No At least 20 litters/dose group for mice, rats or hamsters are available. At least 12 litters /dose group for rabbits are available (three test groups and control group).
3. ✓ ✓ At the high dose, maternal effects are reported as significant (or a limit dose is given, 1,000 mg/kg).
4. * ✓ ✓ At the low dose, no developmental toxicity is reported.
5. ✓ ✓ Dosing duration is at least during the period of major organogenesis, but may extend up to one day prior to term.
6. * No Analysis for test material stability, homogeneity and concentration in dosing medium
7. ✓ ✓ Individual daily observations.
8. ✓ ✓ Individual body weights.
9. ✓ No Individual food consumption.
10. ✓ ✓ Necropsy on all animals
11. ✓ ✓ Individual uterine examination including number of fetal deaths, early and late resorptions and numbers of viable fetuses per sex.
12. ✓ ✓ All ovaries examined to determine number of corpora lutea.
13. ✓ ✓ Individual litter weights and/or individual fetal weights per sex/litter.
14. ✓ ✓ Individual fetus external examination.
15. ✓ No Individual fetus skeletal examination for 1/3 to 1/2 of each litter for rodents and all for all rabbits. ea
16. ✓ No Individual fetus soft tissue examination.

- ~~20~~ all rat fetuses examined
- # of pregnant rabbits < 12/gpp (10 & 11)
- food consumption not measured in rabbits
- each fetus not examined (they examined for fetal abn. and they examined for visceral abnormalities)

Criteria marked with a * are supplemental and may not be required for every study.

Study F CIC/2/

83-4 Reproduction (rat)

ACCEPTANCE CRITERIA

3 generation

Does your study meet the following acceptance criteria?:

1. ✓ Technical form of the active ingredient tested.
2. no At least 20 males and sufficient females to yield 20 pregnant /dose group no
3. no At least 3 dose groups and a control.
4. no At the high dose, parental toxicity is observed (or a limit dose is given, 1,000 mg/kg/day).
5.* no At the low dose, no reproductive effects are observed.
6.* no Analysis for test material stability, homogeneity and concentration in dosing medium
7. no P_1 animals 8 weeks old at the start of the study.
8. ✓ Dosing is continuous starting with the P_1 animals until an individual animal is sacrificed.
9. no Mating is 1 male to 1 female.
10. ✓ The mating period is not more than 3 weeks.
11. ✓ At least two generations are bred.
12. no Individual daily observations.
13. ✓ Individual body weights.
14. ✓ Individual food consumption.
15. ✓ Individual litter observations.
16. no Individual litter weights (pup weights) at birth and on days 4, 7 (optional), 14 and 21 (d 4, 14, 21)
17.* no Sacrifice schedule, all mating males immediately after last mating, all breeding females immediately after weaning last litter, all animals not used for breeding immediately after weaning. termination schedule, not reported
18.* ✓ Necropsy on all animals
19.* no Histopathology of reproductive organs from all animals on the high dose and control P_1 and F_1 animals selected for mating. Animals from all other dosing groups if histological effects are observed at the high dose. not done for females
20.* no Histopathology of all organs with gross lesions.

* 2 studies summarized - first study involved 2 dose groups and a control.
- RBCchE inhibited at 100ppm in one study but not measured in the second study where HDT was 200ppm.
evidence of effect on mating performance and pregnancy
- ages estimated as being 4-5wks
- male female ratio was 1:2 in the first study
- daily observation of test animals not specified

Criteria marked with a * are supplemental and may not be required for every study.

83-5 Chronic Feeding/Oncogenicity in the Rat

ACCEPTANCE CRITERIA

Does your study meet the following acceptance criteria?:

1. ___ Technical form of the active ingredient tested.
2. no ___ At least 50 rats/sex/group (3 test groups and control group). 45 rats/sex/grp
3. ___ Dosing duration is at least 24 months.
4. ___ Number of survivors in any group does not fall below 50% at 18 months or 25% at 24 months.
5. ‡ ___ Doses tested include an MTD or limit dose if nontoxic (1000 mg/kg).
6. • no ___ Doses tested include a NOEL. low dose moderate depression in plasma ChE level
7. • no ___ Analysis for test material stability, homogeneity and concentration in dosing medium
8. ___ Individual daily observations.
9. ___ Individual body weights.
10. ___ Individual or cage food consumption.
11. • ___ Opthalmoscopic examination (at least pertest and at term) control and high dose.
12. ___ Clinical pathology data for at least 10 rats/group consisting of 13, 14 & 15
13. ___ Hematology at 6 month intervals consisting of at least;
    - ___ Erythrocyte count
    - ___ Hemoglobin
    - ___ Hematocrit
    - ___ Leucocyte count
    - •___ Differential count
    - ___ Platelet count (or clotting measure)
14. no ___ Clinical chemistry at 6 month intervals consisting of at least; - clinical chemistry involved only blood + plasma
    - ___ Alkaline phosphatase
    - ___ Aspartate aminotransferase
    - •___ Creatinine kinase
    - ___ Lactic dehydrogenase
    - ___ Glucose
    - ___ Bilirubin
    - ___ Cholesterol
    - •___ Creatinine
    - ___ Total Protein
    - ___ Albumin
    - ___ Urea
    - ___ Inorganic phosphate
    - ___ Calcium
    - •___ Potassium
    - ___ Sodium
    - •___ Chloride

    ChE taken from 10 rats (5M + 5F) per grp.
15. no ___ Urinalysis at 6 month intervals consisting of at least; No urinalysis
    - ___ Blood
    - ___ Protein
    - ___ Ketone bodies
    - ___ Appearance
    - ___ Glucose
    - ___ Total bilirubin
    - •___ Urobilirubin
    - ___ Sediment
    - ___ Specific gravity (osmolality)
    - •___ Volume
16. ___ Individual necropsy of all animals. no 8m + 5F /group not subjected to necropsy (decedents)
17. no ___ Histopathology of the following tissues performed on all nonrodents and rodents, all control and high dose animals, all animals that died or were killed on study, all gross lesions on all animals, target organs on all animals and lungs, liver and kidneys on all other animals.
    - no ___ aorta
    - ___ jejunum
    - ___ peripheral nerve

Criteria marked with a • are supplemental and may not be required for every study.

‡ 7. - homogeneity not formally assessed

17. - Testes and brain collected but not weighed.

___ eyes	___ bone marrow	___ kidneys†
___ caecum	___ liver†	___ esophagus
___ colon	___ lung†	___ ovaries†
___ duodenum	___ lymph nodes	___ oviduct
___ brain†	___ stomach	___ pancreas
___ skin	___ mammary gland	___ rectum
___ heart†	___ spleen†	___ spinal cord (3x)
___ testes†	___ musculature	___ thyroid / parathyroids
___ pituitary	___ epididymis	___ salivary glands
___ ileum	___ adrenals†	___ thymus
___ trachea	___ uterus	___ urinary bladder

† *organs to be weighed.*

‡ The position document entitled "Selection of a Maximum Tolerated Dose (MTD) in Oncogenicity Studies (EPA No. 540/09-88-003) stated EPA's criteria for determining if an oncongenicity study has been adequately performed in terms of doses tested. However OPP is also aware that older oncogenicity studies, upon initial review or re-review. may have been tested at doses lower than the predicted MTD. In the event that such testing appears to be at doses less than the predicted MTD, the Office of Pesticides Program has been reviewing and considering the entire weight of the evidence to determine if retesting is necessary. Certain factors which affect the agency's decision to retest include but are not limited to the following: demonstrated oncogenicity in another species, nearness to the apparent MTD, genotoxic effects, structure-activity factors, absolute value of the highest dose tested and metabolic considerations.

* eyes, skin, aorta, lymph nodes, mammary gland, muscle, esophagus, oviduct and rectum only examined if grossly abnormal
brain and testes not weighed

Criteria marked with a * are supplemental and may not be required for every study.

84-2 Mutagenicity Studies

ACCEPTANCE CRITERIA

Does your study meet the following acceptance criteria?:

General Requirements

1. ____ Technical form of the active ingredient tested.
2. ____ Negative, solvent and/or vehicle control(s) for the test system.
3. ____ Positive control(s) for the test system.
4. ____ Fully identified test system, species, strain, source etc.
5. ____ Fully described method for maintaining test system.
6. ____ Fully described method for preparing test environment and administering test compond.
7. ____ Fully described metabolic activation system, if required.
8. ____ Determination of maximum and range of concentrations/doses used under test conditions.
9.*____ Criteria for determination of a positive effect.

Test Specific Requirements

Salmonella reverse mutation assay

1. ____ Minimum of four strains, TA98, TA100, TA1535 and TA1536. (alternatives need rationale)
2. ____ Strain specific positive controls.
3. ____ Highest concentration limited by toxicity, solubility or 5000 ug/plate.
4.*____ At least 5 different concentrations of test material at adequate intervals.
5.*____ A single positive response confirmed by testing over a narrow range of concentrations.
6.*____ At least three plates experimantal point.

Gene mutation in somatic cells in culture

1. ____ Highest concentration limited by toxicity (10-20% relative survival), solubility or 5000 ug/ml.
2.*____ At least 4 different concentrations of test material to yield a concentration related toxic effect.
3. ____ Determination of the number of cell cultures used.

In vitro mammalian cytogenetics

1. ____ Highest concentration limited by toxicity (e.g. reduced mitotic activity; alteration of cell cycle; cytotoxicity), solubility or 5000 ug/ml.
2.*____ Multiple concentrtions used to define the response.
3.*____ At least two independent cultures for each experimental point.
4. ____ Determination of culture harvest time.

In vivo mammalian cytogenetics - bone marrow

1. ____ At least 5 male and 5 female animals per experimental group.
2. ____ Highest dose limited by toxicity or 5000 mg/kg.
3. ____ Determination of sampling times.

Aberrations; a) one treatment - 3 times in range of 6-48 hours after treatment adequately spaced with central sample at 24 hour (may be altered based on cell cycle time). b) repeated treatments - samples taken 6 and 24 hours after last treatment (may be

Criteria marked with a * are supplemental and may not be required for every study.

altered based on cell cycle time).

Micronucleus; Samples taken 3 times, starting not earlier than 12 hours after the last treatment and at appropriate intervals following the first sample, but not beyond 72 hours.

4. ___ Micronucleus assay, at least 1000 polychromatic erythrocytes/animal scored. Ratio of poly to normochromatic determined by counting 200-1000 erythrocytes (1000 OECD).

Rodent dominant lethal assay

1. ___ Sufficient number of dosed males to provide a minimum of 30 pregnant females per mating interval.
2. ___ Concurrent positive control or results from positive control conducted within 12 months in same laboratory with same strain.
3. ___ Highest dose produced toxicity or 5000 mg/kg.
4. ___ Sampling or exposure over entire spermatogenesis cycle of dosed males (8 weeks mice, 10 weeks rats)

Any mutagenicity test with suggestive or greater positive results/activity shall be submitted reqardless of missing essential items.

85-1 Metabolism Studies

ACCEPTANCE CRITERIA

Does your study meet the following acceptance criteria?:

1. ___ Analytically pure grade of the active ingredient.
2. ___ Isotopically labeled in the core of the molecule and/or significant portions thereof.

-OR-

3. ___ Analytical procedures sufficiently specific and sensitive to identify the test substance.
4. ___ Young adult rats. Other mammalian species may be used for specific purposes.
5. ___ Five male and five female rats for each dose, 4 if following OECD protocol.
6. ___ Two doses, the low to be without effect and the high to produce toxic or pharmacological * signs but not severe effects or mortality.
7. *___ Dosing group A, single low dose by intravenous route (not required if insoluble in water or normal saline).
8. ___ Dosing group B, single low dose by oral route.
9. ___ Dosing group C, 14 consecutive daily low dose of the unlabeled test material by oral route followed by a single low dose of the labeled test material.
10. ___ Dosing group D, single high dose by oral route.
11. ___ Collect individually all urine, feces and expired air for 7 days after labeled dose or until 90+ percent of the dose is excreted (whichever occurs first). Expired air not required if a pilot study shows no excretion in 24 hours.
12. ___ For dosing groups B, C and D, quantity of label in the following tissues and organs;

___ bone	___ liver
___ brain	___ lung
___ fat	___ blood
___ testes	___ muscle
___ heart	___ spleen
___ kidney	___ residual carcass

___ tissues showing pathology in this or prior studies

For all dosing groups:

13. ___ Quantities of label in urine, feces and expired air (if detected in preliminary study) at appropriate intervals (e.g. 4, 8, 12 and 24 hours, 1.5, 2, 3, 4, 5, 6 and 7 days.
14. ___ Qualitative analysis of urine and feces to detect metabolism and identify metabolites (pooled urine and feces by dosing group may be used).

NOTE The metabolism data requirement may be filled in part. For example performing the analysis on a single dose group can satisfy the requirement for that dose.

Criteria marked with a * are supplemental and may not be required for every study.

IRVING MAUER PH...
12/10/90

PHASE FOUR REVIEW

(**NOTE:** This only contains additions and changes from the phase 2 response.)

Pesticide:

Transmitted to HED on: Chemical#/Case#: PIRIMIPHOS-METHYL
Tox, Chem #: Sponsor: ICI

CRM: Phone#:

Branch: Tox-I Reviewer: [signature]

Completed: 12/10/90 Concurrence:

Are there any changes from the reviews in phase 2? ____ NO ✓ YES (See below)

Response, by Guideline

Guideline #: 81-1 Acute oral/rat

MRID_____ **Study #**_____
Discussion/Recommendation:

Guideline #: 81-2 Acute dermal/rabbit

MRID_____ **Study #**_____
Discussion/Recommendation:

Guideline #: 81-3 Acute inhalation/rat

MRID_____ **Study #**_____
Discussion/Recommendation:

Guideline #: 81-4 Primary eye irritation/rabbit

MRID_____ **Study #**_____
Discussion/Recommendation:

Guideline #: 81-5 Primary dermal irritation/rabbit

MRID_____ **Study #**_____
Discussion/Recommendation:

Guideline #: 81-6 Dermal sensitization/Guinea Pig

MRID_____ Study #_____
Discussion/Recommendation:

Guideline #: 81-7 Acute delayed neurotoxicity/hen

MRID_____ Study #_____
Discussion/Recommendation:

Guideline #: 82-1a 90-day feeding/rodent
MRID_____ **Study #**_____
Discussion/Recommendation:

Guideline #: 82-1b 90-day feedubq/nonrodent

MRID_____ **Study #**_____
Discussion/Recommendation:

Guideline #: 82-2 21 Day dermal/rodent/rabbit

MRID_____ **Study #**_____
Discussion/Recommendation:

Guideline #: 82-3 — 90-day dermal/rodent

MRID_____ **Study #**_____
Discussion/Recommendation:

Guideline #: 82-4 — 90-Day inhalation/rat

MRID_____ **Study #**_____
Discussion/Recommendation

Guideline #: 82-5 — 90-day neurotoxicity

MRID_____ **Study #**_____
Discussion/Recommendation:

Guideline #: 83-1a — Chronic toxicity/rodent

MRID_____ **Study #**_____
Discussion/Recommendation:

Guideline #: 83-1b — Chronic toxicity/nonrodent

MRID_____ **Study #**_____
Discussion/Recommendation:

Guideline #: 83-2a — Oncogenicity/rat

MRID_____ **Study #**_____
Discussion/Recommendation:

Guideline #: 83-2b Oncogenicity/mouse

MRID_____ Study #_____
Discussion/Recommendation:

Guideline #: 83-3a Teratology/rat

MRID_____ Study #_____
Discussion/Recommendation:

Guideline #: 83-3b Teratology/rabbit

MRID_____ Study #_____
Discussion/Recommendation:

Guideline #: 83-4 Two-generation reproduction/rat

MRID_____ Study #_____
Discussion/Recommendation:

Guideline #: 84-2a Mutagenicity/Ames

MRID 144969 (92147-024) Study # YV 1226 (Rpt. CTL/P/962)
Discussion/Recommendation: Phase-3 Summary Response appears to be acceptable for a 1989 study

Guideline #: 84-2b Mutagenicity/Struct. Chromosomal Aberration (Dominant lethal - mi

MRID 41556302 Study # CTL/C/291
Discussion/Recommendation:
Phase 3 Summary Response alludes to major deficiencies (*) in this 1975 assay which would render it unacceptable.

(*) Not certain technical was tested; details of animal care/husbandry absent; no indication top dose was toxic (NOT a MTD).

Guideline #: 84-~~X~~-2 Gene mutation in mammalian cells ~~Other genotoxic effects~~

MRID 41556303 Study # CTL/C/1437

Discussion/Recommendation: This Phase 3 Summary Response indicates this 1985 assay was carried out under criteria which would render it acceptable.

Guideline #: 85-1 Metabolism

MRID_____ Study #_____

Discussion/Recommendation:

Guideline #: 85-2 Dermal penetration

MRID_____ Study #_____

Discussion/Recommendation:

Guideline #: 86-1 Domestic animal safety

MRID_____ Study #_____

Discussion/Recommendation:

fluvalinate milky

81-1 Acute Oral Toxicity in the Rat

ACCEPTANCE CRITERIA

MRID#s 00126257, 00164523

Does your study meet the following acceptance criteria?:

1. NC Technical form of the active ingredient tested. (for reregistration only)
2.* ___ At least 5 young adult rats/sex/group
3. ___ Dosing, single oral.
4.* ___ Vehicle control if other than water.
5. ___ Doses tested, sufficient to determine a toxicity category or a limit dose (5000 mg/kg).
6. ___ Individual observations for the entire day of dosing.
7. ___ Observation period to last at least 14 days, or until all test animals appear normal whichever is longer.
8. ___ Individual daily observations.
9.* ___ Individual body weights.
10.* ___ Gross necropsy on all animals.

Criteria marked with a * are supplemental and may not be required for every study.

81-2 Acute Dermal Toxicity in the Rat, Rabbit or Guinea Pig

ACCEPTANCE CRITERIA

MRID#s 00126257 and 00164523

Does your study meet the following acceptance criteria?:

1. NO Technical form of the active ingredient tested. (for reregistration only)
2.*___ At least 5 animals/sex/group
3.*___ Rats 200-300 gm, rabbits 2.0-3.0 kg or guinea pigs 350-450 gm.
4. ___ Dosing, single dermal.
5. ___ Dosing duration at least 24 hours.
6.*___ Vehicle control, only if toxicity of vehicle is unknown.
7. ___ Doses tested, sufficient to determine a toxicity category or a limit dose (2000 mg/kg).
8. ___ Application site clipped or shaved at least 24 hours before dosing
9. ___ Application site at least 10% of body surface area.
10. ___ Application site covered with a porous nonirritating cover to retain test material and to prevent ingestion.
11. ___ Individual observations for the entire day of dosing.
12. ___ Observation period to last at least 14 days, or until all test animals appear normal whichever is longer.
13. ___ Individual daily observations.
14.*___ Individual body weights.
15.*___ Gross necropsy on all animals.

Criteria marked with a * are supplemental and may not be required for every study.

81-3 Acute Inhalation Toxicity in the Rat

ACCEPTANCE CRITERIA

MRID# 00126258

Does your study meet the following acceptance criteria?:

1. NO Technical form of the active ingredient tested. (for reregistration only)
2. ____ Product is a gas, a solid which may produce a significant vapor hazard based on toxicity and expected use or contains particles of inhalable size for man (aerodynamic diameter 15 um or less).
3. *____ At least 5 young adult rats/sex/group
4. *____ Dosing, at least 4 hours by inhalation.
5. *____ Chamber air flow dynamic, at least 10 air changes/hour, at least 19% oxygen content.
6. ____ Chamber temperature, 22° C (±2°), relative humidity 40-60%.
7. ____ Monitor rate of air flow
8. ____ Monitor actual concentrations of test material in breathing zone.
9. ____ Monitor aerodynamic particle size for aerosols.
10. ____ Doses tested, sufficient to determine a toxicity catagory or a limit dose (5 mg/L actual concentration of respirable substance).
11. ____ Individual observations for the entire day of dosing.
12. ____ Observation period to last at least 14 days, or until all test animals appear normal whichever is longer.
13. ____ Individual daily observations.
14. *____ Individual body weights.
15. *____ Gross necropsy on all animals.

Criteria marked with a * are supplemental and may not be required for every study.

81-4 Primary Eye Irritation in the Rabbit

ACCEPTANCE CRITERIA

MRID# 00126257 and 00164524

Does your study meet the following acceptance criteria?:

1. NO Technical form of the active ingredient tested. (for reregistration only)
2. ____ Study not required if material is corrosive, causes severe dermal irritation or has a pH of ≤ 2 or ≥ 11.5.
3.* ____ 6 adult rabbits
4. ____ Dosing, instillation into the conjunctival sac of one eye per animal.
5.* ____ Dose, 0.1 ml if a liquid; 0.1 ml or not more than 100 mg if a solid, paste or particulate substance.
6. ____ Solid or granular test material ground to a fine dust.
7. ____ Eyes not washed for at least 24 hours.
8. ____ Eyes examined and graded for irritation before dosing and at 1, 24, 48 and 72 hr, then daily until eyes are normal or 21 days (whichever is shorter).
9. ____ Individual observations for the entire day of dosing.
10. ____ Individual daily observations.

Criteria marked with a * are supplemental and may not be required for every study.

81-5 Primary Dermal Irritation Study
ACCEPTANCE CRITERIA

MRID#s 00126257 and 00164524

Does your study meet the following acceptance criteria?:

1. No Technical form of the active ingredient tested. (for reregistration only)
2. ____ Study not required if material is corrosive or has a pH of $\leq$ 2 or $\geq$ 11.5.
3.* ____ 6 adult animals.
4. ____ Dosing, single dermal.
5. ____ Dosing duration 4 hours.
6. ____ Application site shaved or clipped at least 24 hour prior to dosing.
7. ____ Application site approximately 6 cm^2.
8. ____ Application site covered with a gauze patch held in place with nonirritating tape
9. ____ Material removed, washed with water, without trauma to application site
10. ____ Application site examined and graded for irritation at 1, 24, 48 and 72 hr, then daily until normal or 14 days (whichever is shorter).
11. ____ Individual observations for the entire day of dosing.
12. ____ Individual daily observations.

Criteria marked with a * are supplemental and may not be required for every study.

81-6 Dermal Sensitization in the Guinea Pig

ACCEPTANCE CRITERIA

MRID # 00129341

Does your study meet the following acceptance criteria?:

1. ✓ Technical form of the active ingredient tested. (for reregistration only)
2. — Study not required if material is corrosive or has a pH of ≤ 2 or ≥ 11.5.
3. ✓ One of the following methods is utilized;
   - ___ Freund's complete adjuvant test
   - ___ Guinea pig maximization test
   - ___ Split adjuvant technique
   - ✓ Buehler test
   - ___ Open epicutaneous test
   - ___ Maur optimization test
   - ___ Footpad technique in guinea pig
   - ___ Other test accepted by OECD (specify)_____
4. ✓ Complete description of test
5. NO Reference for test.
6. ? Test followed essentially as described in reference document.
7. NO Positive control included.

Criteria marked with a * are supplemental and may not be required for every study.

81-7 Acute Neurotoxicity in the Hen

ACCEPTANCE CRITERIA

Study #1 MRID#/Acc#NA DER study #ICI/49/75220, 8/11/75 Study #2 MRID#/Acc#NA Huntingdon 6/20/80

Does your study meet the following acceptance criteria?:

1. √ + Study performed on an organophosphate cholinesterase inhibiting compound.
2. √ + Technical form of the active ingredient tested.
3. * √ + Positive control utilized.
4. √ + Species utilized, domestic laying hen 8-14 months of age.
5. √ + Dosing oral by gavage or capsule (dermal or inhalation may be used).
6. √ + An acute oral LD_{50} is determined.
7. No + Dose tested equal to an acute oral LD_{50} or a limit test of 5000 mg/kg.
8. * √ + Dosed animals may be protected with atropine and/or 2-PAM.
9. √ ? Sufficient test animals so that at least 6 survive.
10. √ + Negative (vehicle) control group of at least 6 hens
11. √ + Positive control of at least 4 hens. (if used)
12. No No Test dose repeated if no signs of delayed neurotoxicity observed by 21 days after dosing.
13. √ + Observation period 21 days after each dose.
14. ? ? Individual daily observations.
15. ? ? Individual body weights.
16. * ? ? Individual necropsy not required.
17. No ? Histopathology performed on all animals. Tissue to be fixed <u>in situ</u> using whole animal perfusion techniques. At least three sections of each of the following tissues:

____brain, including medulla oblongata
____spinal cord; upper cervical, mid-thoracic and lumbro-sacral regions
____tibial nerve; proximal regions and branches
____sciatic nerve

Criteria marked with a * are supplemental and may not be required for every study.

82-1 Subchronic Feeding in the Rodent and Nonrodent

ACCEPTANCE CRITERIA

Rat ✓ MRID#/Acc# NA Dog + MRID#/Acc# NA

Does your study meet the following acceptance criteria?:

1. ✓ + Technical form of the active ingredient tested.
2. ✓ + At least 10 rodents or 4 nonrodents/sex/group (3 test groups and control group).
3. ✓ + Dosing duration daily for 90-days or 5 days/week for 13 weeks.
4. ✓ + Doses tested include signs of toxicity at high dose but no lethality in nonrodents or a limit dose if nontoxic (1000 mg/kg).
5. ✓ NO Doses tested include a NOEL.
6. •? ? Analysis for test material stability, homogeneity and concentration in dosing medium
7. ? ? Individual daily observations.
8. ? ? Individual body weights.
9. ? ? Individual or cage food consumption.
10. •? ? Opthalmoscopic examination (at least pretest and at term) control and high dose.
11. ✓ + Clinical pathology data of 12 & 13 at termination for rodents, before, monthly or midway and at termination for nonrodents.
12. ✓ + Hematology.
    - ___ Erythrocyte count
    - ___ Hemoglobin
    - ___ Hematocrit
    - ___ Leucocyte count
    - •___ Differential count
    - ___ Platelet count (or clotting measure)
13. ✓ + Clinical chemistry.
    - ___ Alkaline phosphatase
    - ___ Aspartate aminotransferase
    - •___ Creatinine kinase
    - ___ Lactic dehydrogenase
    - ___ Glucose
    - ___ Bilirubin
    - ___ Cholesterol
    - •___ Creatinine
    - ___ Total Protein
    - ___ Albumin
    - ___ Urea
    - ___ Inorganic phosphate
    - ___ Calcium
    - •___ Potassium
    - ___ Sodium
    - •___ Chloride
14. •NO + Urinalysis, only when indicated by expected or observed activity. As scheduled in 11.
    - ___ Blood
    - ___ Protein
    - ___ Ketone bodies
    - ___ Appearance
    - ___ Glucose
    - ___ Total bilirubin
    - •___ Urobilirubin
    - ___ Sediment
    - ___ Specific gravity (osmolality)
    - •___ Volume
15. ? ? Individual necropsy of all animals.
16. ? ? Histopathology of the following tissues performed on all nonrodents and rodents, all control and high dose animals, all animals that died or were killed on study, all gross lesions on all animals, target organs on all animals and lungs, liver and kidneys on all other animals.

Criteria marked with a • are supplemental and may not be required for every study.

____ aorta	____ jejunum	____ peripheral nerve
____ eyes	____ bone marrow	____ kidneys†
____ caecum	____ liver†	____ esophagus
____ colon	____ lung†	____ ovaries†
____ duodenum	____ lymph nodes	____ oviduct
____ brain†	____ stomach	____ pancreas
____ skin	____ mammary gland	____ rectum
____ heart†	____ spleen†	____ spinal cord (3x)
____ testes†	____ musculature	____ thyroid / parathyroids
____ pituitary	____ epididymis	____ salivary glands
____ ileum	____ adrenals†	____thymus
____ trachea	____ uterus	____urinary bladder

† organs to be weighed

Criteria marked with a * are supplemental and may not be required for every study.

82-2 Repeated Dose Dermal Toxicity (21-day) in the Rat, Rabbit or Guinea Pig

ACCEPTANCE CRITERIA

MRID# 00129342

Does your study meet the following acceptance criteria?:

1. ✓ Technical form of the active ingredient tested.
2. ✓ At least 5 animals/sex/group (3 test groups and control group).
3. ✓ Dosing duration at least 6 hour/day for 21 days or 5 days/week for 3 weeks.
4. ? Application site at least 10% of body surface area.
5. ✓ Doses tested include signs of toxicity at high dose, no or minimal dermal irritation, minimal lethality or a limit dose (1000mg/kg) if nontoxic.
6. * NO Doses tested include a NOEL.
7. ? Individual daily observations.
8. ? Individual body weights.
9. ✓ Individual or cage food consumption.
10. ✓ Clinical pathology data of 11 & 12 at termination.
11. ✓ Hematology.
    - ✓ Erythrocyte count
    - ✓ Hemoglobin
    - ✓ Hematocrit
    - ✓ Leucocyte count
    - * ✓ Differential count
    - ✓ Platelet count (or clotting measure)
12. ✓ Clinical chemistry.
    - ✓ Alkaline phosphatase
    - ✓ Aspartate aminotransferase
    - * ___ Creatinine kinase
    - ✓ Lactic dehydrogenase
    - ✓ Glucose
    - ✓ Bilirubin
    - ✓ Cholesterol
    - * ___ Creatinine
    - ✓ Total Protein
    - ✓ Albumin
    - ✓ Urea
    - ___ Inorganic phosphate
    - ✓ Calcium
    - * ✓ Potassium
    - ✓ Sodium
    - * ___ Chloride
13. * ___ Urinalysis, only when indicated by expected or observed activity. As scheduled in 10.
    - ___ Blood
    - ___ Protein
    - ___ Ketone bodies
    - ___ Appearance
    - ___ Glucose
    - ___ Total bilirubin
    - * ___ Urobilirubin
    - ___ Sediment
    - ___ Specific gravity (osmolality)
    - * ___ Volume
14. ✓ Individual necropsy of all animals.
15. ✓ Histopathology performed on all control and high dose animals, all animals that died or were killed on study consisting of all gross lesions on all animals, target organs on all animals (to determine a NOEL), and skin (normal and treated) lungs, liver and kidneys.

Criteria marked with a * are supplemental and may not be required for every study.

82-3 Repeated Dose Dermal Toxicity (90-day) in the Rat, Rabbit or Guinea Pig

ACCEPTANCE CRITERIA

Does your study meet the following acceptance criteria?:

1. ____ Technical form of the active ingredient tested.
2. ____ At least 10 animals/sex/group (3 test groups and control group).
3. ____ Dosing duration at least 6 hour/day daily for 90 days or 5 days/week for 13 weeks.
4. ____ Application site at least 10% of body surface area.
5. ____ Doses tested include signs of toxicity at high dose, no or minimal dermal irritation, minimal lethality or a limit dose (1000mg/kg) if nontoxic.
6. *____ Doses tested include a NOEL.
7. ____ Individual daily observations.
8. ____ Individual body weights.
9. ____ Individual or cage food consumption.
10. *____ Opthalmoscopic examination (at least pretest and at term) control and high dose.
11. ____ Clinical pathology data of 12 & 13 in all animals at termination.
12. ____ Hematology.
    - ____ Erythrocyte count
    - ____ Hemoglobin
    - ____ Hematocrit
    - ____ Leucocyte count
    - *____ Differential count
    - ____ Platelet count (or clotting measure)
13. ____ Clinical chemistry.
    - ____ Alkaline phosphatase
    - ____ Aspartate aminotransferase
    - *____ Creatinine kinase
    - ____ Lactic dehydrogenase
    - ____ Glucose
    - ____ Bilirubin
    - ____ Cholesterol
    - *____ Creatinine
    - ____ Total Protein
    - ____ Albumin
    - ____ Urea
    - ____ Inorganic phosphate
    - ____ Calcium
    - *____ Potassium
    - ____ Sodium
    - *____ Chloride
14. *____ Urinalysis, only when indicated by expected or observed activity. As scheduled in 11.
    - ____ Blood
    - ____ Protein
    - ____ Ketone bodies
    - ____ Appearance
    - ____ Glucose
    - ____ Total bilirubin
    - *____ Urobilirubin
    - ____ Sediment
    - ____ Specific gravity (osmolality)
    - *____ Volume
15. ____ Individual necropsy of all animals.
16. ____ Histopathology of the following tissues performed on all nonrodents and rodents, all control and high dose animals, all animals that died or were killed on study, all gross lesions on all animals, target organs on all animals and lungs, liver and kidneys on all other animals.
    - ____ aorta
    - ____ eyes
    - ____ jejunum
    - ____ bone marrow
    - ____ peripheral nerve
    - ____ kidneys‡

Criteria marked with a * are supplemental and may not be required for every study.

____ caecum	____ liver†	____ esophagus
____ colon	____ lung†	____ ovaries†
____ duodenum	____ lymph nodes	____ oviduct
____ brain†	____ stomach	____ pancreas
____ skin	____ mammary gland	____ rectum
____ heart†	____ spleen†	____ spinal cord (3x)
____ testes†	____ musculature	____ thyroid / parathyroids
____ pituitary	____ epididymis	____ salivary glands
____ ileum	____ adrenals†	____ thymus
____ trachea	____ uterus	____ urinary bladder

† organs to be weighed

82-4 Subchronic Inhalation Toxicity (90-day) in the Rat

ACCEPTANCE CRITERIA

Does your study meet the following acceptance criteria?:

1. ____ Technical form of the active ingredient tested. (for reregistration only)
2. ____ Product is a gas, a solid which may produce a significant vapor hazard based on toxicity and expected use or contains particles of inhalable size for man (aerodynamic diameter 15 um or less).
3. ____ At least 10 young adult rats/sex/group
4. ____ Dosing, 6 hours per day, 5 days per week for 13 weeks.
5. ____ Food and water should be withheld during dosing.
6. *____ Chamber air flow dynamic, at least 10 air changes/hour, at least 19% oxygen content.
7. ____ Chamber temperature, 22° C (±2°), relative humidity 40-60%.
8. *____ Alternatively, oro-nasal or head only exposures may be used.
9. ____ Monitor rate of air flow,
10. ____ Monitor actual concentrations of test material in breathing zone.
11. ____ Monitor aerodynamic particle size for aerosols.
12. ____ Individual daily observations.
13. ____ Individual body weights.
14. ____ Individual or cage food consumption.
15. *____ Opthalmoscopic examination (at least pretest and at term) control and high dose.
16. ____ Clinical pathology data of 17 & 18 in all animals at termination.
17. ____ Hematology.
    - ____ Erythrocyte count
    - ____ Hemoglobin
    - ____ Hematocrit
    - ____ Leucocyte count
    - *____ Differential count
    - ____ Platelet count (or clotting measure)
18. ____ Clinical chemistry.
    - ____ Alkaline phosphatase
    - ____ Aspartate aminotransferase
    - *____ Creatinine kinase
    - ____ Lactic dehydrogenase
    - ____ Glucose
    - ____ Bilirubin
    - ____ Cholesterol
    - *____ Creatinine
    - ____ Total Protein
    - ____ Albumin
    - ____ Urea
    - ____ Inorganic phosphate
    - ____ Calcium
    - *____ Potassium
    - ____ Sodium
    - *____ Chloride
19. *____ Urinalysis, only when indicated by expected or observed activity. As scheduled in 16.
    - ____ Blood
    - ____ Protein
    - ____ Ketone bodies
    - ____ Appearance
    - ____ Glucose
    - ____ Total bilirubin
    - *____ Urobilirubin
    - ____ Sediment
    - ____ Specific gravity (osmolality)
    - *____ Volume

Criteria marked with a * are supplemental and may not be required for every study.

20. ____ Individual necropsy of all animals.
21. ____ Histopathology of the following tissues performed on all nonrodents and rodents, all control and high dose animals, all animals that died or were killed on study, all gross lesions on all animals, target organs on all animals and lungs, liver and kidneys on all other animals.

____ aorta	____ jejunum	____ peripheral nerve
____ eyes	____ bone marrow	____ kidneys†
____ caecum	____ liver†	____ esophagus
____ colon	____ lung†	____ ovaries†
____ duodenum	____ lymph nodes	____ oviduct
____ brain†	____ stomach	____ pancreas
____ skin	____ mammary gland	____ rectum
____ heart†	____ spleen†	____ spinal cord (3x)
____ testes†	____ musculature	____ thyroid / parathyroids
____ pituitary	____ epididymis	____ salivary glands
____ ileum	____ adrenals†	____ thymus
____ trachea	____ uterus	____ urinary bladder

† organs to be weighed

82-5 Subchronic Neurotoxicity (90-day) in the Hen

ACCEPTANCE CRITERIA

MRID# 00126254

Does your study meet the following acceptance criteria?:

1. ✓ Study performed on an organophosphate cholinesterase inhibiting compound.
2.* ✓ Technical form of the active ingredient tested.
3. ✓ Positive control utilized. (recommended but optional)
4. ✓ Species utilized, domestic laying hen 8-14 months of age.
5. ✓ At least 10 animals/sex/group [3 test groups, a positive control (optional) and a negative (vehicle) control group].
6. ✓ Dosing duration at least daily for 90 days or 5 days/week for 13 weeks.
7. ✓ Dose route oral gavage or capsule. (dermal or inhalation may be appropriate)
8. ✓ Doses tested include signs of toxicity at high dose, no or minimal lethality
9.* ✓ Doses tested include a NOEL.
10. ? Individual daily observations.
11. ? Individual body weights.
12. ? Individual or cage food consumption.
13.* — Individual necropsy not required.
14. ND Histopathology performed on all animals. Tissue to be fixed in situ using whole animal perfusion techniques. At least three sections of each of the following tissues:

    ____ brain, including medulla oblongata
    ____ spinal cord; upper cervical, mid-thoracic and lumbro-sacral regions
    ____ tibial nerve; proximal regions and branches
    ____ sciatic nerve

Criteria marked with a * are supplemental and may not be required for every study.

83-1 Chronic Feeding in the Rodent and Nonrodent

ACCEPTANCE CRITERIA

Nonrodent MRID#/ACC# NA DER study#? Hunlyden 5/8/93

Does your study meet the following acceptance criteria?:

1. ✓ Technical form of the active ingredient tested.
2. ✓ At least 20 rodents or 4 nonrodents/sex/group (3 test groups and control group).
3. ✓ Dosing duration in rodents minimum 12 month nonfood use, 24 months food use; in nonrodents minimum 12 months[1].
4. ✓ Doses tested include signs of toxicity at high dose but no lethality in nonrodents or a limit dose if nontoxic (1,000 mg/kg).
5. • ND Doses tested include a NOEL.
6. • ? Analysis for test material stability, homogeneity and concentration in dosing medium
7. ? Individual daily observations.
8. ? Individual body weights.
9. ? Individual or cage food consumption.
10. • ? Opthalmoscopic examination (at least pertest and at term) control and high dose.
11. ? Clinical pathology data for all nonrodents and at least 10 rodents/group consisting of 12, 13 & 14.
13. ? Hematology at 6 month intervals consisting of at least;
    - ___ Erythrocyte count
    - ___ Hemoglobin
    - ___ Hematocrit
    - ___ Leucocyte count
    - •___ Differential count
    - ___ Platelet count (or clotting measure)
14. ? Clinical chemistry at 6 month intervals consisting of at least;
    - ___ Alkaline phosphatase
    - ___ Aspartate aminotransferase
    - •___ Creatinine kinase
    - ___ Lactic dehydrogenase
    - ___ Glucose
    - ___ Bilirubin
    - ___ Cholesterol
    - •___ Creatinine
    - ___ Total Protein
    - ___ Albumin
    - ___ Urea
    - ___ Inorganic phosphate
    - ___ Calcium
    - •___ Potassium
    - ___ Sodium
    - •___ Chloride
15. ? Urinalysis at 6 month intervals consisting of at least;
    - ___ Blood
    - ___ Protein
    - ___ Ketone bodies
    - ___ Appearance
    - ___ Glucose
    - ___ Total bilirubin
    - •___ Urobilirubin
    - ___ Sediment
    - ___ Specific gravity (osmolality)
    - •___ Volume
16. ? Individual necropsy of all animals.
17. ? Histopathology of the following tissues performed on all nonrodents and rodents, all control and high dose animals, all animals that died or were killed on study, all gross lesions on all animals, target organs on all animals and lungs, liver and kidneys on all other animals.

Criteria marked with a • are supplemental and may not be required for every study.

___ eyes	___ bone marrow	___ kidneys†
___ caecum	___ liver†	___ esophagus
___ colon	___ lung†	___ ovaries†
___ duodenum	___ lymph nodes	___ oviduct
___ brain†	___ stomach	___ pancreas
___ skin	___ mammary gland	___ rectum
___ heart†	___ spleen†	___ spinal cord (3x)
___ testes†	___ musculature	___ thyroid / parathyroids
___ pituitary	___ epididymis	___ salivary glands
___ ileum	___ adrenals†	___ thymus
___ trachea	___ uterus	___ urinary bladder

† organs to be weighed
* Six month dog studies may be acceptable. (?)

Criteria marked with a * are supplemental and may not be required for every study.

83-2 Oncogenicity in Rats or Mice

ACCEPTANCE CRITERIA

Mice MRID#/Acc# NA DER of study # ICI 3417658 ; 7/15/76

1. ✓ Technical form of the active ingredient tested.
2. ✓ At least 50 animals/sex/group (3 test groups and control group).
3. ✓ Dosing duration is at least 18 months for mice and 24 months for rats.
4. ? Number of survivors in any group does not fall below 50% at 15 months for mice, 18 months for rats or 25% at 18 months for mice, 24 months for rats.
5. ‡ ✓ Doses tested include an MTD or limit dose if nontoxic (1,000 mg/kg).
6. * ✓ Doses tested include a NOEL for systematic effects.
7. * ? Analysis for test material stability, homogeneity and concentration in dosing medium
8. ? Individual daily observations.
9. ? Individual body weights.
10. ? Individual or cage food consumption.
11. ? Individual necropsy of all animals.
12. ? Blood smear from 10 animals/sex/dose at 12 and 18 months and termination. Differential count high dose and controls, all other doses if high dose shows pathology.
13. ? Histopathology of the following tissues performed on all interim sacrifice animals, all control and high dose animals, all animals that died or were killed on study, all gross lesions on all animals, target organs on all animals and lungs, liver and kidneys on all other animals.

___ aorta	___ jejunum	___ peripheral nerve
___ eyes	___ bone marrow	___ kidneys†
___ caecum	___ liver†	___ esophagus
___ colon	___ lung†	___ ovaries†
___ duodenum	___ lymph nodes	___ oviduct
___ brain†	___ stomach	___ pancreas
___ skin	___ mammary gland	___ rectum
___ heart†	___ spleen†	___ spinal cord (3x)
___ testes†	___ musculature	___ thyroid / parathyroids
___ pituitary	___ epididymis	___ salivary glands
___ ileum	___ adrenals†	___ thymus
___ trachea	___ uterus	___ urinary bladder

† organs to be weighed

‡ The position document entitled "Selection of a Maximum Tolerated Dose (MTD) in Oncogenicity Studies (EPA No. 540/09-88-003) stated EPA's criteria for determining if an oncongenicity study has been adequately performed in terms of doses tested. However OPP is also aware that older oncogenicity studies, upon initial review or re-review. may have been tested at doses lower than the predicted MTD. In the event that such testing appears to be at doses less than the predicted MTD, the Office of Pesticides Program has been reviewing and

Criteria marked with a * are supplemental and may not be required for every study.

considering the entire weight of the evidence to determine if retesting is necessary. Certain factors which affect the agency's decision to retest include but are not limited to the following: demonstrated oncogenicity in another species, nearness to the apparent MTD, genotoxic effects, structure-activity factors, absolute value of the highest dose tested and metabolic considerations.

83-3 Teratology Studies

ACCEPTANCE CRITERIA

MRID# 00151623 (not √) (rabbit +) MRID#/Acc# NA DER Rev # #0/CTL/P/119 B; 7/74

Does your study meet the following acceptance criteria?:

1. √ + Technical form of the active ingredient tested.
2. √ no At least 20 litters/dose group for mice, rats or hamsters are available. At least 12 litters /dose group for rabbits are available (three test groups and control group).
3. √ + At the high dose, maternal effects are reported as significant (or a limit dose is given, 1,000 mg/kg).
4.* √ + At the low dose, no developmental toxicity is reported.
5. √ + Dosing duration is at least during the period of major organogenesis, but may extend up to one day prior to term.
6.* √ ? Analysis for test material stability, homogeneity and concentration in dosing medium
7. ? ? Individual daily observations.
8. ? ? Individual body weights.
9. ? ? Individual food consumption.
10. √ ? Necropsy on all animals
11. √ ? Individual uterine examination including number of fetal deaths, early and late resorptions and numbers of viable fetuses per sex.
12. √ ? All ovaries examined to determine number of corpora lutea.
13. √ ? Individual litter weights and/or individual fetal weights per sex/litter.
14. √ ? Individual fetus external examination.
15. √ ? Individual fetus skeletal examination for 1/3 to 1/2 of each litter for rodents and all for all rabbits.
16. √ ? Individual fetus soft tissue examination.

Criteria marked with a * are supplemental and may not be required for every study.

83-4 Reproduction

ACCEPTANCE CRITERIA

(Rat #1) MRID#/Acc# NA DER study #547/72/853; 12/7/72 (Rat #2 +) MRID#/Acc# NA DER# study # ICI 63/76534

Does your study meet the following acceptance criteria?:

1. ✓ + Technical form of the active ingredient tested.
2. NO + At least 20 males and sufficient females to yield 20 pregnant /dose group
3. NO + At least 3 dose groups and a control.
4. NO + At the high dose, parental toxicity is observed (or a limit dose is given, 1,000 mg/kg/day).
5.* NO + At the low dose, no reproductive effects are observed.
6.* ? ? Analysis for test material stability, homogeneity and concentration in dosing medium
7. ? ? P_1 animals 8 weeks old at the start of the study.
8. ? ? Dosing is continuous starting with the P_1 animals until an individual animal is sacrificed.
9. NO + Mating is 1 male to 1 female.
10. ? ? The mating period is not more than 3 weeks.
11. ✓ + At least two generations are bred.
12. ? ? Individual daily observations.
13. ? ? Individual body weights.
14. ? ? Individual food consumption.
15. ? ? Individual litter observations.
16. ? ? Individual litter weights (pup weights) at birth and on days 4, 7 (optional), 14 and 21 .
17.* ? ? Sacrifice schedule, all mating males immediately after last mating, all breeding females immediately after weaning last litter, all animals not used for breeding immediately after weaning.
18.* ? ? Necropsy on all animals
19.* ? ? Histopathology of reproductive organs from all animals on the high dose and control P_1 and F_1 animals selected for mating. Animals from all other dosing groups if histological effects are observed at the high dose.
20.* ? ? Histopathology of all organs with gross lesions.

Criteria marked with a * are supplemental and may not be required for every study.

83-5 Chronic Feeding/Oncogenicity in the Rat

MRID#/Acc# NA

ACCEPTANCE CRITERIA

DER Study # HO/IH/P/113; 6/74

Does your study meet the following acceptance criteria?:

1. ✓ Technical form of the active ingredient tested.
2. NO At least 50 rats/sex/group (3 test groups and control group).
3. ✓ Dosing duration is at least 24 months.
4. ? Number of survivors in any group does not fall below 50% at 18 months or 25% at 24 months.
5. ‡ ✓ Doses tested include an MTD or limit dose if nontoxic (1000 mg/kg).
6. * ✓ Doses tested include a NOEL.
7. * ? Analysis for test material stability, homogeneity and concentration in dosing medium
8. ? Individual daily observations.
9. ? Individual body weights.
10. ? Individual or cage food consumption.
11. * ? Opthalmoscopic examination (at least pertest and at term) control and high dose.
12. NO Clinical pathology data for at least 10 rats/group consisting of 13, 14 & 15
13. ✓ Hematology at 6 month intervals consisting of at least;
    - ___ Erythrocyte count
    - ✓ Leucocyte count
    - ✓ Hemoglobin
    - * ✓ Differential count
    - ✓ Hematocrit
    - ✓ Platelet count (or clotting measure)
14. ✓ Clinical chemistry at 6 month intervals consisting of at least;
    - ___ Alkaline phosphatase
    - ___ Total Protein ✓ ChE
    - ___ Aspartate aminotransferase
    - ___ Albumin
    - * ___ Creatinine kinase
    - ___ Urea
    - ___ Lactic dehydrogenase
    - ___ Inorganic phosphate
    - ___ Glucose
    - ___ Calcium
    - ___ Bilirubin
    - * ___ Potassium
    - ___ Cholesterol
    - ___ Sodium
    - * ___ Creatinine
    - * ___ Chloride
15. ___ Urinalysis at 6 month intervals consisting of at least;
    - ___ Blood
    - ___ Total bilirubin
    - ___ Protein
    - * ___ Urobilirubin
    - ___ Ketone bodies
    - ___ Sediment
    - ___ Appearance
    - ___ Specific gravity (osmolality)
    - ___ Glucose
    - * ___ Volume
16. ? Individual necropsy of all animals.
17. ? Histopathology of the following tissues performed on all nonrodents and rodents, all control and high dose animals, all animals that died or were killed on study, all gross lesions on all animals, target organs on all animals and lungs, liver and kidneys on all other animals.
    - ___ aorta
    - ___ jejunum
    - ___ peripheral nerve

Criteria marked with a * are supplemental and may not be required for every study.

____ eyes	____ bone marrow	____ kidneys†
____ caecum	____ liver†	____ esophagus
____ colon	____ lung†	____ ovaries†
____ duodenum	____ lymph nodes	____ oviduct
____ brain†	____ stomach	____ pancreas
____ skin	____ mammary gland	____ rectum
____ heart†	____ spleen†	____ spinal cord (3x)
____ testes†	____ musculature	____ thyroid / parathyroids
____ pituitary	____ epididymis	____ salivary glands
____ ileum	____ adrenals†	____ thymus
____ trachea	____ uterus	____ urinary bladder

† organs to be weighed.

‡ The position document entitled "Selection of a Maximum Tolerated Dose (MTD) in Oncogenicity Studies (EPA No. 540/09-88-003) stated EPA's criteria for determining if an oncongenicity study has been adequately performed in terms of doses tested. However OPP is also aware that older oncogenicity studies, upon initial review or re-review. may have been tested at doses lower than the predicted MTD. In the event that such testing appears to be at doses less than the predicted MTD, the Office of Pesticides Program has been reviewing and considering the entire weight of the evidence to determine if retesting is necessary. Certain factors which affect the agency's decision to retest include but are not limited to the following: demonstrated oncogenicity in another species, nearness to the apparent MTD, genotoxic effects, structure-activity factors, absolute value of the highest dose tested and metabolic considerations.

84-2 Mutagenicity Studies

MRID# 00144969 (Amo. ✓)

ACCEPTANCE CRITERIA

(cytogenetic +) -MRID# NA/Acc# 071451/OER rating # 412212

Does your study meet the following acceptance criteria?:

General Requirements

1. ✓ + Technical form of the active ingredient tested.
2. ✓ + Negative, solvent and/or vehicle control(s) for the test system.
3. ✓ + Positive control(s) for the test system.
4. ✓ ? Fully identified test system, species, strain, source etc.
5. ✓ ? Fully described method for maintaining test system.
6. ✓ ? Fully described method for preparing test environment and administering test compound.
7. ✓ ? Fully described metabolic acitvation system, if required.
8. ✓ ? Determination of maximum and range of concentrations/doses used under test conditions.
9.* NO ? Criteria for determination of a positive effect.

Test Specific Requirements

Salmonella reverse mutation assay

1. ✓ Minimum of four strains, TA98, TA100, TA1535 and TA1536. (alternatives need rationale)
2. ✓ Strain specific positive controls.
3. ✓ Highest concentration limited by toxicity, solubility or 5000 ug/plate.
4.* ✓ At least 5 different concentrations of test material at adequate intervals.
5.* ✓ A single positive response confirmed by testing over a narrow range of concentrations.
6.* ✓ At least three plates experimantal point.

Gene mutation in somatic cells in culture

1. ___ Highest concentration limited by toxicity (10-20% relative survival), solubility or 5000 ug/ml.
2.* ___ At least 4 different concentrations of test material to yield a concentration related toxic effect.
3. ___ Determination of the number of cell cultures used.

In vitro mammalian cytogenetics

1. ___ Highest concentration limited by toxicity (e.g. reduced mitotic activity; alteration of cell cycle; cytotoxicity), solubility or 5000 ug/ml.
2.* ___ Multiple concentrtions used to define the response.
3.* ___ At least two independent cultures for each experimental point.
4. ___ Determination of culture harvest time.

In vivo mammalian cytogenetics - bone marrow

1. ___ NO At least 5 male and 5 female animals per experimental group.
2. ___ NO Highest dose limited by toxicity or 5000 mg/kg.
3. ___ ? Determination of sampling times.

Aberrations; a) one treatment - 3 times in range of 6-48 hours after treatment adequately spaced with central sample at 24 hour (may be altered based on cell cycle time). b) repeated treatments - samples taken 6 and 24 hours after last treatment (may be

Criteria marked with a * are supplemental and may not be required for every study.

altered based on cell cycle time).

Micronucleus; Samples taken 3 times, starting not earlier than 12 hours after the last treatment and at appropriate intervals following the first sample, but not beyond 72 hours.

4. ____ Micronucleus assay, at least 1000 polychromatic erythrocytes/animal scored. Ratio of poly to normochromatic determined by counting 200-1000 erythrocytes (1000 OECD).

Rodent dominant lethal assay

1. ____ Sufficient number of dosed males to provide a minimum of 30 pregnant females per mating interval.
2. ____ Concurrent positive control or results from positive control conducted within 12 months in same laboratory with same strain.
3. ____ Highest dose produced toxicity or 5000 mg/kg.
4. ____ Sampling or exposure over entire spermatogenesis cycle of dosed males (8 weeks mice, 10 weeks rats)

Any mutagenicity test with suggestive or greater positive results/activity shall be submitted reqardless of missing essential items.

85-1 Metabolism Studies

ACCEPTANCE CRITERIA

MRID# 00129345

Does your study meet the following acceptance criteria?:

1. ? Analytically pure grade of the active ingredient.
2. ✓ Isotopically labeled in the core of the molecule and/or significant portions thereof.

-OR-

3. ? Analytical procedures sufficiently specific and sensitive to identify the test substance.
4. ✓ Young adult rats. Other mammalian species may be used for specific purposes.
5. NC Five male and five female rats for each dose, 4 if following OECD protocol.
6. NO Two doses, the low to be without effect and the high to produce toxic or pharmacological signs but not severe effects or mortality.
7.* NO Dosing group A, single low dose by intravenous route (not required if insoluble in water or normal saline).
8. NO Dosing group B, single low dose by oral route.
9. ✓ Dosing group C, 14 consecutive daily low dose of the unlabeled test material by oral route followed by a single low dose of the labeled test material.
10. NO Dosing group D, single high dose by oral route.
11. ✓ Collect individually all urine, feces and expired air for 7 days after labeled dose or until 90+ percent of the dose is excreted (whichever occurs first). Expired air not required if a pilot study shows no excretion in 24 hours.
12. NO For dosing groups B, C and D, quantity of label in the following tissues and organs;

___ bone	✓ liver
___ brain	___ lung
✓ fat	___ blood
___ testes	✓ muscle
___ heart	___ spleen
✓ kidney	___ residual carcass
___ tissues showing pathology in this or prior studies	

For all dosing groups:

13. ✓ Quantities of label in urine, feces and expired air (if detected in preliminary study) at appropriate intervals (e.g. 4, 8, 12 and 24 hours, 1.5, 2, 3, 4, 5, 6 and 7 days.
14. NO Qualitative analysis of urine and feces to detect metabolism and identify metabolites (pooled urine and feces by dosing group may be used).

NOTE The metabolism data requirement may be filled in part. For example performing the analysis on a single dose group can satisfy the requirement for that dose.

Criteria marked with a * are supplemental and may not be required for every study.

SRRD/GCSB TRANSMITTAL SHEET FOR PART B's

Pesticide: Pirimiphos-methyl

Transmitted to HED on 11-28-89 Chemical#/Case#: 2535
Chem. Tox.#: 3348
Sponsor: ICI Americas

CRM: Ruby Whitters Phone#: 557- 2557

✓ This action contains a request for a DATA WAIVER ( )/ TIME EXTENSION ( ). Label attached: Yes ( )/ No (X)

Branch: Toxicology I, Section II Reviewer: William B. Greear
Completed: / / Concurrence:

Response, by Guideline

Guideline #: 81-1 Description: Acute oral/rat
Compliance Codes: Y/1 Data Waiver ( )/ Time Extension ( )
MRID 00080726, Study # NA
Discussion: MRID# 00080726 not in bibliography. MRID# 00126257 conducted on a 75.4% formulation. Tox. category III. MRID# 00164523 conducted on a 40% formulation. Technical is 94.2%.

Recommendation: A study conducted on the technical is required for review

Guideline #: 81-2 Description: Acute Dermal/rat
Compliance Codes: Y/1 Data Waiver ( )/ Time Extension ( )
MRID 00080727, Study # NA
Discussion: MRID# 00080727 not in bibliography. MRID# 00126257 conducted on a 75.4% formulation. Tox category III. MRID# 00164523 conducted on a 40% formulation. Technical is 94.2%

Recommendation: A study conducted on the technical is required for review.

Guideline #: 81-3 Description: Acute Inhalation/rat
Compliance Codes: Y/1 Data Waiver ( )/ Time Extension ( )
MRID 00126258, Study # CTL/P/602
Discussion: MRID# 00126258 was not conducted on technical. Conducted on a 75.4% formulation. Tox category not established. Nominal concentration reported. Technical is 94.2%.

Recommendation : A study conducted on the technical is required for review.

Guideline #: 81-4 Description: Primary Eye Irritation/rabbit
Compliance Codes: Y/1 Data Waiver ( )/ Time Extension ( )
MRID 00164524, Study # CTL/P/1305
Discussion: MRID# 00164524 conducted on a 40% formulation. MRID# 00126257 conducted on a 75.4% formulation. Tox category II for 75.4% formulation. MRID# 00080729 not in bibliography. Technical is 94.2%.

Recommendation : A study conducted on the technical is required for review.

Guideline #: 81-5 Description: Primary dermal irritation/rabbit
Compliance Codes: Y/1 Data Waiver ( )/ Time Extension ( )
MRID 00080728, Study # NA
Discussion: MRID# 00080728 not in bibliography. MRID# 00126257 conducted on a 75.4% formulation. Tox. category III. MRID# 00164524 conducted on a 40% formulation. Technical is 94.2%

Recommendation : A study conducted on the technical is required for review.

Guideline #: 81-6 Description: Dermal sensitization/guinea pig
Compliance Codes: Y/1 Data Waiver ( )/ Time Extension ( )
MRID 00129341, Study # CTL/P/999
Discussion: DER of MRID# 00129341 has been examined and appears to be adequate (Core-Minimum).

Recommendation : The study MRID# 00129341 is acceptable for review.

Guideline #: 81-7 Description: Acute delayed neurotoxicity/hen
Compliance Codes: Y/1 Data Waiver ( )/ Time Extension ( )
MRID 00080721, Study # NA
Discussion: MRID# 00080721 not in bibliography and not in one-liners. Two studies (#s JCI/49/75220 and no# dated 6/20/80) present in TOX files. Both studies are unacceptable. Results were uninterpretable, but suggestive of a positive response.

Recommendation : A study is not needed because the 90-day neurotoxicity study supersedes the acute study.

Guideline #: 82-1(a) Description: 90-day feeding/rodent
Compliance Codes: Y/1 Data Waiver ( )/ Time Extension ( )
MRID 00080730, Study # NA
Discussion: MRID#s 00080730 and 00080745 not in bibliography. A 90-day rat study was listed in the one-liners. (Core-minimum). The DER was examined but was too brief to determine the adequacy of study. However, the 2-Yr chronic/oncogenicity study supersedes the requirement for the study.

Recommendation : The study is not needed for review

Guideline #: 82-1(b) Description: 90-day feeding/nonrodent
Compliance Codes: Y/1 Data Waiver ( )/ Time Extension ( )
MRID 00080742, Study # NA
Discussion: MRID#S 00080742 and 00080743 not in bibliography. A 90-day dog study is listed in the out-of-date (Core-minimum). The DER was examined but found to be too brief to determine the adequacy of the study. However, a 2-yr chronic study supersedes the requirement for this study.

Recommendation : The study is not needed for review.

Guideline #: 82-2 Description: 21-day dermal/rodent/rabbit
Compliance Codes: Y/1 Data Waiver ( )/ Time Extension ( )
MRID 00129342, Study # 2279-38/59
Discussion: DER of MRID# 00 129342 has been examined and appears to be adequate (Core-Minimum).

Recommendation : The study MRID# 00129342 is acceptable for review.

Guideline #: 82-3 Description: 90-day dermal/rodent
Compliance Codes: N/7 Data Waiver ( )/ Time Extension ( )
MRID NA Study # NA
Discussion: The study is not required under current use patterns. Code 7 indicates "criteria not met"

Recommendation : A study is not needed.

Guideline #: 82-4 Description: 90-day inhalation/rodent
Compliance Codes: N/I Data Waiver ( )/ Time Extension ( )
MRID NA, Study # NA
Discussion: A study is not required under current use patterns. Code 7 indicates "criteria not met".

Recommendation : A study is not needed.

Guideline #: 82-5(a) Description: 90-day neurotoxicity/hen
Compliance Codes: Y/I Data Waiver ( )/ Time Extension ( )
MRID 00126254, Study # ICI 411 NT/821118
Discussion: DER of MRID# 00126254 has been reviewed and appears to be acceptable (Core - guideline.)

Recommendation : The study MRID# 00126254 is acceptable for review.

Guideline #: 82-5(b) Description: 90-day neurotoxicity/ mammalian
Compliance Codes: N/I Data Waiver ( )/ Time Extension ( )
MRID NA, Study # N/A
Discussion: Code 7 indicates "criteria not met"

Recommendation : Study is not needed at this time.

Start

Guideline #: 83-1(a) Description: Chronic feeding/rodent
Compliance Codes: Y/1 Data Waiver ( )/ Time Extension ( )
MRID 00081912, Study # NA
Discussion: MRID # 00081912 was not in the bibliography. However a 2-Yr Chronic/Oncogenic study is listed in the one-liners. The DER has been examined (Study # HO/IH/P/113; 4/74) but was too brief to determine the adequacy of the study. (Core - minimum)

Recommendation : The study should be submitted for review after being reformatted.

Guideline #: 83-1(b) Description: Chronic feeding/nonrodent
Compliance Codes: Y/1 Data Waiver ( )/ Time Extension ( )
MRID 00080749, Study # NA
Discussion: MRID # 00080749 was not in the bibliography. However, a 2-Yr Chronic study conducted by Hunterdon Res on 5/8/73 is listed in the one-liners. DER of study was examined but is too brief to determine the adequacy of the study. (Core-guideline)

Recommendation : The study should be submitted for review after being reformatted.

Guideline #: 83-2(a) Description: Oncogenicity/rat
Compliance Codes: Y/1 Data Waiver ( )/ Time Extension ( )
MRID 00081912, Study # NA
Discussion: Same as 83-1(a)

Recommendation : Same as 83-1(a)

Guideline #: 83-2(b) Description: Oncogenicity/mouse
Compliance Codes: Y/1 Data Waiver ( )/ Time Extension ( )
MRID 00080746, Study # NA
Discussion: MRID # 00080746 was not in the bibliography, NCEA or 18-Mo Mouse study (# ICI 3417658; 7/15/78) is listed in the one-liner. File DER was examined but is too brief to determine the adequacy of the study (Core-minimum)

Recommendation : The study should be submitted for review after being reformatted.

Guideline #: 83-3(a) Description: Teratogenicity/rat
Compliance Codes: Y/1 Data Waiver ( )/ Time Extension ( )
MRID 00151623, Study # CTL/P/1334
Discussion: DER of MRID # 00151623 has been examined and appears to be acceptable. (Core-guideline.)

Recommendation : The study MRID # 00151623 is acceptable for review.

Guideline #: 83-3(a) Description: Teratogenicity/rat
Compliance Codes: / Data Waiver ( )/ Time Extension ( )
MRID _____, Study # _____
Discussion:

Recommendation :

Guideline #: 83-3(b). Description: Teratogenicity/rabbit.
Compliance Codes: Y/1 Data Waiver ( )/ Time Extension ( )
MRID 00080734, Study # NA
Discussion: Start MRID # 00080734 not in bibliography. However a rabbit study is listed on the one-liners (Study # HC/CTL/P/1198). (Core - Minimum) DER of the study has been examined but is too brief to determine the adequacy of the study.

Recommendation : The study MRID # 00080734 should be reformatted and submitted for review.

Guideline #: 83-3(c) Description: Teratogenicity/mouse
Compliance Codes: NA/NA Data Waiver ( )/ Time Extension ( )
MRID NA, Study # NA
Discussion: NA

Recommendation : NA

Guideline #: 83-4 Description: 3-generation reprod./rat
Compliance Codes: Y/1 Data Waiver ( )/ Time Extension ( )
MRID 00080735, Study # 5457/72/853
Discussion: MRID #'s 00080735 and 00080736 are not in the bibliography. One study is listed on the one-liners (#ICI 63/76534; 8/31/76) and is Core-minimum. A second study (#5457/72/853) is in a Tox memo 2/21/80 and is Core-Minimum. DER have been examined but contain too little detail to determine if the studies are adequate.

Recommendation : The two studies MRID #'s 00080735 and 00080736 should be submitted for review after being reformatted.

Guideline #: 84-2(a) Description: Gene mutation/ Ames
Compliance Codes: Y/1 Data Waiver ( )/ Time Extension ( )
MRID 00144969, Study # CTL/P/962
Discussion: DER of MRID# 00144969 has been examined and appears to be acceptable. (Acceptable)

Recommendation : The study MRID# 00144969 is acceptable for review.

Guideline #: 84-2(b) Description: Struct. chrom. aberration
Compliance Codes: Y/1 Data Waiver ( )/ Time Extension ( )
MRID 00126256, Study # NA
Discussion: MRID#s 00126256 and 00080733 are not in the bibliography. A cytogenetic study in rats (study # 412212, 5/80) is on file-Utera. (No Core-grade) DER was examined but was too brief to determine the adequacy of the study.

Recommendation : The study should be submitted for review after being reformatted.

Guideline #: 84-2(c) Description: Other genotoxic effects
Compliance Codes: Y/4 Data Waiver ( )/ Time Extension ( )
MRID NA, Study # NA
Discussion: A new study will be submitted.

Recommendation : The new study will be acceptable for review.

Guideline #: 85-1 Description: General metabolism/rat
Compliance Codes: Y/1 Data Waiver ( )/ Time Extension ( )
MRID 00129345, Study # ICI 299/79565
Discussion: MRID #s 00050738 and 00080737 not in bibliography. DER of MRID # 00129345 has been examined and appears to be a low-dose repeated-dose study. The single low and high-dose portions of the study have not been conducted. (Core-minimum)

Recommendation: The study is acceptable for review as a low-dose repeated-dose study. An additional study is required for a single low- and high-dose dosing regimens. Study should be reformatted.

Guideline #: 85-2 Description: Dermal penetration
Compliance Codes: N/7 Data Waiver ( )/ Time Extension ( )
MRID NA, Study # NA
Discussion: Code 7 indicates "Criteria not met". However, it was once proposed to use the chemical to control fleas on carpet. It was decided, after receiving an exposure assessment, that a dermal penetration study was necessary is pursued.

Recommendation: The study ~~is~~ will be needed if the once proposed use for carpet treatment to control fleas

Guideline #: 86-1 Description: Domestic animal safety
Compliance Codes: N /NA Data Waiver ( )/ Time Extension ( )
MRID NA, Study # NA
Discussion: The sponsor failed to indicate a response. However, it was once proposed to use the chemical to control fleas on carpets. Domestic animals would probably receive a significant exposure.

Recommendation: The study will be needed, if the once proposed use for carpet treatment to control fleas is pursued.

13544

011665

Chemical:	**Pirimiphos-methyl (ANSI)**
PC Code:	**108102**
HED File Code	**13000 Tox Reviews**
Memo Date:	**04/04/90**
File ID:	**00000000**
Accession Number:	**412-02-0007**

HED Records Reference Center
05/22/2002